Urinary Biomarkers and Risk of ESRD in the Atherosclerosis Risk in Communities Study


Abstract

Background and objectives Liver fatty acid binding protein (L-FABP), kidney injury molecule 1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and neutrophil gelatinase–associated lipocalin (NGAL) are urinary markers of tubular injury that may also be markers of chronic kidney damage. We evaluated the association of these markers with incident ESRD in a community-based sample from the Atherosclerosis Risk in Communities Study.

Design, setting, participants, & measurements This was a matched case-control study of 135 patients with ESRD and 186 controls who were matched on sex, race, kidney function, and diabetes status at baseline (Atherosclerosis Risk in Communities Study visit 4, 1996–1998). Urinary KIM-1 indexed to creatinine (Cr), NAG/Cr, NGAL/Cr, and L-FABP/Cr were measured in stored spot urine samples from the baseline examination. Associations of KIM-1/Cr, NAG/Cr, and NGAL/Cr with patients with incident ESRD through 2008 were modeled continuously and categorically (quartiles) using conditional logistic regression. L-FABP/Cr was modeled only categorically because of a large number of measurements below the lower limit of detection for the assay (2.4 ng/ml).

Results No significant associations were observed for NAG/Cr, NGAL/Cr, or L-FABP/Cr with ESRD. Those in the highest category for KIM-1/Cr had a higher risk of ESRD compared with those with undetectable biomarker levels (reference group) in unadjusted models (odds ratio, 2.24; 95% confidence interval, 1.97 to 4.69; P=0.03) or adjustment for age (odds ratio, 2.23; 95% confidence interval, 1.06 to 4.67; P=0.03). This association was attenuated with additional adjustment for baseline kidney function (odds ratio, 2.02; 95% confidence interval, 0.95 to 4.31; P=0.07 after additional adjustment for eGFR and natural log of the urinary albumin-to-creatinine ratio). No association between KIM-1/Cr and ESRD was found when KIM-1/Cr was analyzed as a continuous variable.

Conclusions Elevated urinary KIM-1/Cr may be associated with a higher risk of incident ESRD, but it does not add to risk prediction after accounting for traditional markers of kidney function in this population.


Introduction

CKD is common in the United States and associated with higher risk of mortality, cardiovascular disease, and progression to ESRD (1–4). The few well established biomarkers for risk stratification in CKD (e.g., serum creatinine and cystatin C and urinary albumin) may not adequately capture risk, particularly at early stages of disease. Identifying new biomarkers associated with CKD progression has the potential to enhance identification of high-risk patients and improve outcomes in CKD.

Several urinary markers of tubular injury associated with AKI may also have clinical utility as markers of chronic kidney damage and are under investigation as markers of CKD and CKD progression (5–8). As part of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) CKD Biomarkers Consortium, we sought to determine whether levels of urinary biomarkers liver fatty acid binding protein (L-FABP), kidney injury molecule 1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and neutrophil gelatinase–associated lipocalin (NGAL) are associated with incident ESRD in a nested case-control study of adults from the Atherosclerosis Risk in Communities (ARIC) Study.

Materials and Methods

Study Population

The ARIC Study is a prospective, community–based study of 15,792 adults ages 45–64 years old recruited from four United States communities (Forsyth County, North Carolina; Minneapolis, Minnesota; Washington County, Maryland; and Jackson, Mississippi) and examined in 1987–1989 (9). Follow-up visits occurred in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), and 2011–2013 (visit 5). Visit 4 was selected as the baseline visit for this study, because spot urine samples were collected and stored at −70°C. Participants who were free of ESRD at visit 4 and had available serum
creatine–based eGFR, diabetes status, and urinary albumin-
to-creatinine ratio (UACR) measurements were eligible for this
case-control study. Black participants at centers in Min-
neapolis, Minnesota and Washington County, Maryland were
excluded because of small numbers; in Jackson, Mississippi, only black participants were recruited. The Institutional Re-
view Boards at all ARIC Study sites reviewed and approved
the study protocol, including banking of spot urine samples
for future studies.

Matching Factor and Covariate Assessment

Kidney function and participant characteristics selected
as matching factors were assessed at the ARIC Study visit 4.
Both blood and spot urine samples were collected from
participants during the clinic visit. Serum creatinine was
measured using a modified Jaffe method and calibrated to
the assay performed at the Cleveland Clinic. eGFR was sub-
sequently calculated using the 2009 Chronic Kidney Disease
Epidemiology Collaboration (CKD-EPI) Equation (10).
UACR (milligrams per gram) was determined from urinary
albumin and creatinine measured in the spot urine samples.
Diabetes was defined as the presence of a fasting blood
glucose ≥126 mg/dl, the presence of a nonfasting blood
glucose ≥200 mg/dl, a self-reported history of diabetes, or
a self-reported use of medication for diabetes.

Case Definition and Selection of Patients and Controls

Cases included incident ESRD events after visit 4 identi-
fied through hospitalization surveillance through December 31,
2008. Incident ESRD cases were defined as (1) hospitaliza-
tions with International Classification of Diseases, Ninth Re-
vision, Clinical Modification codes specified for kidney
transplant or ESRD or a procedural code indicating dialysis
(excluding those with a concomitant code for AKI) and (2)
deaths with corresponding International Classification of
Diseases, Tenth Revision, Clinical Modification codes speci-
fied for ESRD or kidney failure, excluding those with AKI
codes unless there was a concomitant history of CKD (11–14).
Controls were frequency matched to patients on the basis
of the following criteria at visit 4: (1) eGFR category on the
basis of the CKD-EPI Equation (<45, 45–59, 60–74, 75–89,
90–105, or ≥105 mL/min per 1.73 m²), (2) UACR category
(<30, 30–299, or ≥300 mg/g), (4) diabetes status, (4) sex,
and (5) race. Overall, 185 patients with incident ESRD and
260 controls were identified, of whom 141 patients with
incident ESRD and 209 controls had urine samples avail-
able and measurements for all four biomarkers and urinary
creatinine. For the final analysis, participants in matching
factor strata that included only patients or only controls
(resulting in uninformative strata) were excluded, result-
ing in a final sample size of 135 patients and 186 controls.

Exposure Assessment

The CKD Biomarkers Consortium was established in 2008
by the NIDDK to advance the field of CKD biomarker
discovery and validation. Urinary biomarkers were assayed
at performance laboratories designated by the Consortium
using the visit 4 spot urine samples that had undergone one
freeze-thaw cycle. Urinary albumin was quantified by an
immunoturbidimetric method, creatinine was measured by
a kinetic colorimetric assay on a Roche Automated Analyzer
(Indianapolis, IN), and L-FABP was measured by a two-site
sandwich ELISA assay (CMIC, Tokyo, Japan) at the Univer-
sity of Pennsylvania. At Brigham and Women’s Hospital,
KIM-1 was measured by a microbead–based sandwich
ELISA on a Bioplex-200 Platform (Bio-Rad, Hercules, CA),
and NAG was measured by an enzymatic assay (Roche).
NGAL was measured by a noncompetitive sandwich assay
with chemiluminescent signal detection on an ARCHITECT
Platform (Abbott Diagnostics, Abbott Park, IL) at University
College in Dublin, Ireland.

Statistical Analyses

Baseline characteristics of patients and controls were
compared using t tests for continuous and chi-squared tests
for categorical characteristics. Urinary biomarkers were in-
dexed to urinary creatinine in our primary analyses for con-
sistency with other analyses of urinary biomarkers in the
CKD Biomarkers Consortium (15). KIM-1 indexed to creati-
nine (KIM-1/Cr), NAG/Cr, and NGAL/Cr were evaluated
categorically as quartiles and continuously with a log2 trans-
formation to account for their skewed distributions. Given
the high percentage of participants with L-FABP measure-
ments that were undetectable (0 ng/ml; 29.0%) or measure-
ments >0 ng/ml but below the assay limit of detection
(LOD; 2.4 ng/ml) as determined by the performance labora-
tory during assay validation (21%). L-FABP was evaluated
categorically in regression models: (1) undetectable, (2) detect-
able but below the LOD, (3) above the LOD for L-FABP but
below the median measurement of L-FABP/Cr, or (4) above
the LOD for L-FABP and at or above the median measure-
ments of L-FABP/Cr.

Associations of continuous log–transformed KIM-1/Cr,
NAG/Cr, NGAL/Cr, and L-FABP/Cr (log[L-FABP/Cr+1] to
account for zero values) with continuous participant char-
acteristics were evaluated using Pearson correlation coeffi-
cients. We used conditional logistic regression to estimate
the incidence odds ratio (OR) of ESRD while accounting for
the matching factors. Model adjustment beyond accounting
for matching factors included (1) unadjusted, (2) adjustment
for baseline age, and (3) sequential adjustment for eGFR
(modeled as a linear spline with a knot at 60 ml/min per
1.73 m²) and natural log–transformed UACR to account for
potential residual confounding within baseline kidney func-
tion categories. We determined P trend across quartile, with
biomarker quartile modeled as a linear term. In sensitivity
analyses, we evaluated the association of 1/urinary Cr with
ESRD using conditional logistic regression to determine
whether potential associations observed with biomarkers
indexed to urinary creatinine reflected associations with creat-
inine and not the biomarkers of interest. We also examined
ESRD associations of biomarkers without normalization to
urinary creatinine in conditional logistic regression models.
A P value <0.05 was considered statistically significant, and
analyses were performed using Stata SE, version 12.1.

Results

Study Sample Characteristics

Baseline characteristics of the study population by case
status are presented in Table 1. Patients and controls were of
similar age at baseline and by design, did not differ for the
matching factors sex, race, and diabetes status. Despite
matching on eGFR and albumin-to-creatinine ratio (ACR) groups, patients had lower baseline eGFR and higher baseline ACR than controls. Patients were less likely to have undetectable L-FABP (23.2% versus 32.8%) and more likely than controls to have L-FABP above the LOD (62.2% versus 40.6%). Median KIM-1/Cr, NAG/Cr, and NGAL/Cr levels were significantly higher in patients than in controls. KIM-1/Cr, NAG/Cr, and NGAL/Cr correlated negatively with eGFR and positively with UACR. Weak but significant correlations were observed for NAG/Cr with fasting blood glucose and NGAL/Cr with systolic BP and body mass index (Table 2).

Association of Urinary Biomarkers with Incident ESRD
For the primary analysis, KIM-1, NAG, and NGAL were indexed to urinary creatinine in conditional logistic regression models (Table 3). NAG/Cr and NGAL/Cr were not associated with ESRD when modeled categorically or continuously (Table 3). KIM-1/Cr was not associated with ESRD when modeled continuously, but the highest quartile of KIM-1/Cr was associated with a >2-fold increased odds of incident ESRD when compared with the lowest quartile in unadjusted models (quartile 4 versus quartile 1: hazard ratio, 2.25; 95% CI, 1.08 to 4.70; P=0.03), which was unchanged with adjustment for age (P=0.03) (Table 3). This association was attenuated with additional adjustment for baseline kidney function (OR, 2.14; 95% CI, 1.01 to 4.33; P=0.05 in a model adjusted for baseline eGFR; OR, 2.02; 95% CI, 0.95 to 4.31; P=0.07 after additional adjustment for lnUACR).

Compared with participants with an undetectable L-FABP level, the highest L-FABP/Cr category (≥6.67 ng/mg) was associated with a nonsignificant 2.2 increased odds of incident ESRD compared with undetectable biomarker levels before and after adjustment for age (OR, 2.22; 95% CI, 0.92 to

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics by ESRD case status</th>
</tr>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Age (yr)</td>
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<tr>
<td>Sex, N (%)</td>
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<td>women</td>
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<tr>
<td>Race, N (%)</td>
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<tr>
<td>black</td>
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<tr>
<td>Diabetes, N (%)</td>
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<td></td>
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<tr>
<td>Fasting blood glucose</td>
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<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
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<tr>
<td>eGFR (ml/min per 1.73 m²) group, N (%)</td>
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<tr>
<td>≤44</td>
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<tr>
<td>45–59</td>
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<td>60–74</td>
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<tr>
<td>75–89</td>
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<tr>
<td>90–104</td>
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<tr>
<td>≥105</td>
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<tr>
<td>ACR (mg/g), median (interquartile range)</td>
</tr>
<tr>
<td>ACR (mg/g) group</td>
</tr>
<tr>
<td>&lt;30</td>
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<tr>
<td>30–299</td>
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<tr>
<td>≥300</td>
</tr>
</tbody>
</table>

Normalized urinary biomarkers
L-FABP/Cr
- Undetectable (0 ng/ml): 33 (24.4) vs 60 (32.3), P <0.001
  - Below LOD for L-FABP (>0–2.4 ng/ml): 19 (14.1) vs 50 (26.9)
  - Above LOD and below median detectable (<6.67 ng/ml): 30 (22.2) vs 49 (26.3)
  - Above LOD and above median detectable (≥6.67 ng/ml): 53 (39.3) vs 27 (14.5)
KIM-1/Cr (pg/mg)
- 914 (536–1851) vs 665 (381–1047), P <0.001
NAG/Cr (milliunits/mg)
- 5.6 (3.1–9.9) vs 3.9 (2.5–6.2), P =0.002
NGAL/Cr (ng/mg)
- 30.2 (10.7–86.8) vs 14.8 (8.5–40.2), P <0.001

Raw urinary biomarkers
L-FABP
- Undetectable (0 ng/ml): 33 (24.4) vs 60 (32.6), P <0.001
  - Below LOD (>0–2.4 ng/ml): 19 (14.1) vs 50 (26.9)
  - Above LOD and below median detectable (≥2.4 to <7.59 ng/ml): 31 (23.0) vs 48 (25.8)
  - Above LOD and above median detectable (≥7.59 ng/ml): 52 (38.5) vs 28 (15.0)
KIM-1 (pg/ml)
- 821 (365–1542) vs 573 (299–1233), P =0.03
NAG (milliunits/ml)
- 4.3 (2.3–8.2) vs 3.9 (2.1–6.5), P =0.07
NGAL (ng/ml)
- 24.6 (8.8–77.9) vs 15.1 (7.5–36.0), P =0.001

Continuous characteristics are presented as mean (SD) or median (25th–75th percentile). Categorical characteristics are presented as N (%). ACR, albumin-to-creatinine ratio; L-FABP, urinary liver fatty acid binding protein; Cr, indexed to urinary creatinine; LOD, limit of detection; KIM-1, urinary kidney injury molecule 1; NAG, urinary N-acetyl-β-D-glucosaminidase; NGAL, urinary neutrophil gelatinase–associated lipocalin.
Table 2. Partial Pearson correlations of log_{10}-transformed urinary biomarkers with participant characteristics accounting for urinary creatinine normalization (n=321)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Age</th>
<th>SBP</th>
<th>eGFR</th>
<th>lnUACR</th>
<th>FBG</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-FABP/Cr</td>
<td>0.05</td>
<td>0.24a</td>
<td>−0.56a</td>
<td>0.68a</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>KIM-1/Cr</td>
<td>0.18b</td>
<td>0.17b</td>
<td>−0.33a</td>
<td>0.40b</td>
<td>0.05</td>
<td>−0.03</td>
</tr>
<tr>
<td>NAG/Cr</td>
<td>0.09</td>
<td>0.16b</td>
<td>−0.33a</td>
<td>0.45b</td>
<td>0.17b</td>
<td>0.04</td>
</tr>
<tr>
<td>NGAL/Cr</td>
<td>0.04</td>
<td>0.25a</td>
<td>−0.41a</td>
<td>0.48b</td>
<td>0.005</td>
<td>0.11</td>
</tr>
</tbody>
</table>

SBP, systolic BP; lnUACR, natural log of the urinary albumin-to-creatinine ratio; FBG, fasting blood glucose; BMI, body mass index; L-FABP/Cr, urinary liver fatty acid binding protein indexed to urinary creatinine; KIM-1/Cr, urinary kidney injury molecule 1 indexed to creatinine; NAG/Cr, urinary N-acetyl-β-D-glucosaminidase indexed to creatinine; NGAL/Cr, urinary neutrophil gelatinase-associated lipocalin indexed to creatinine.

\(^\text{a}p<0.001, \ ^\text{b}p<0.01, \ ^\text{c}p=0.07, \ ^\text{d}p=0.28\)
Table 3. Odds ratios and 95% confidence intervals for incident ESRD for urinary biomarkers modeled categorically and continuously indexed to urinary creatinine (n=321)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adjusted for Age</th>
<th>Adjusted for Age and eGFR</th>
<th>Adjusted for Age, eGFR, and lnUACR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
</tr>
<tr>
<td><strong>L-FABP/Cr (ng/mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable (0 ng/ml)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Detectable; below LOD</td>
<td>0.74 (0.35 to 1.53) 0.41</td>
<td>0.74 (0.35 to 1.54) 0.42</td>
<td>0.72 (0.34 to 1.51) 0.38</td>
<td>0.77 (0.36 to 1.62) 0.49</td>
</tr>
<tr>
<td>≥0.97 to &lt;6.67</td>
<td>0.99 (0.48 to 2.03) 0.97</td>
<td>0.99 (0.48 to 2.04) 0.97</td>
<td>0.93 (0.45 to 1.92) 0.85</td>
<td>0.99 (0.48 to 2.07) 0.99</td>
</tr>
<tr>
<td>≥6.67</td>
<td>2.22 (0.92 to 5.33) 0.08</td>
<td>2.20 (0.93 to 5.35) 0.07</td>
<td>1.87 (0.77 to 4.58) 0.17</td>
<td>1.75 (0.71 to 4.30) 0.22</td>
</tr>
<tr>
<td><strong>KIM-1/Cr (pg/mg)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Q1≤432.30</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q2&gt;432.30 to ≤789.69</td>
<td>1.25 (0.63 to 2.50) 0.53</td>
<td>1.25 (0.62 to 2.50) 0.53</td>
<td>1.28 (0.64 to 2.56) 0.49</td>
<td>1.23 (0.61 to 2.47) 0.57</td>
</tr>
<tr>
<td>Q3&gt;789.69 to ≤1214.91</td>
<td>1.23 (0.60 to 2.51) 0.57</td>
<td>1.22 (0.60 to 2.50) 0.58</td>
<td>1.21 (0.59 to 2.50) 0.61</td>
<td>1.26 (0.61 to 2.62) 0.53</td>
</tr>
<tr>
<td>Q4&gt;1214.91</td>
<td>2.25 (1.08 to 4.70) 0.03</td>
<td>2.23 (1.07 to 4.68) 0.03</td>
<td>2.14 (1.01 to 4.53) 0.05</td>
<td>2.02 (0.95 to 4.31) 0.07</td>
</tr>
<tr>
<td>P trend</td>
<td>0.15</td>
<td>0.15</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Continuous (log scale; per SD)</td>
<td>1.30 (0.98 to 1.71) 0.07</td>
<td>1.29 (0.98 to 1.71) 0.07</td>
<td>1.27 (0.95 to 1.68) 0.10</td>
<td>1.24 (0.93 to 1.66) 0.14</td>
</tr>
<tr>
<td><strong>NAG/Cr (milliunits/mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1≤2.69</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q2&gt;2.69 to ≤4.55</td>
<td>1.52 (0.75 to 3.08) 0.24</td>
<td>1.52 (0.75 to 3.09) 0.24</td>
<td>1.44 (0.71 to 2.94) 0.31</td>
<td>1.44 (0.70 to 2.98) 0.32</td>
</tr>
<tr>
<td>Q3&gt;4.55 to ≤7.50</td>
<td>1.41 (0.69 to 2.90) 0.35</td>
<td>1.41 (0.68 to 2.89) 0.35</td>
<td>1.35 (0.65 to 2.78) 0.42</td>
<td>1.31 (0.63 to 2.72) 0.47</td>
</tr>
<tr>
<td>Q4&gt;7.50</td>
<td>2.05 (0.91 to 4.61) 0.08</td>
<td>2.05 (0.91 to 4.62) 0.08</td>
<td>1.89 (0.82 to 4.37) 0.14</td>
<td>1.70 (0.73 to 3.97) 0.22</td>
</tr>
<tr>
<td>P trend</td>
<td>0.11</td>
<td>0.12</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Continuous (log scale; per SD)</td>
<td>1.08 (0.82 to 1.42) 0.57</td>
<td>1.08 (0.82 to 1.42) 0.56</td>
<td>1.03 (0.77 to 1.36) 0.85</td>
<td>0.99 (0.75 to 1.31) 0.93</td>
</tr>
<tr>
<td><strong>NGAL/Cr (ng/mg)</strong></td>
<td></td>
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<tr>
<td>Q1&lt;9.38</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q2&gt;9.38 to ≤18.71</td>
<td>0.75 (0.37 to 1.50) 0.42</td>
<td>0.75 (0.37 to 1.51) 0.42</td>
<td>0.72 (0.36 to 1.45) 0.36</td>
<td>0.67 (0.33 to 1.35) 0.26</td>
</tr>
<tr>
<td>Q3&gt;18.71 to ≤50.75</td>
<td>2.05 (0.98 to 4.28) 0.06</td>
<td>2.04 (0.97 to 4.27) 0.06</td>
<td>2.02 (0.96 to 4.26) 0.06</td>
<td>1.83 (0.87 to 3.88) 0.11</td>
</tr>
<tr>
<td>Q4&gt;50.75</td>
<td>1.57 (0.67 to 3.64) 0.30</td>
<td>1.56 (0.67 to 3.63) 0.30</td>
<td>1.24 (0.52 to 2.96) 0.63</td>
<td>1.00 (0.40 to 2.45) 0.99</td>
</tr>
<tr>
<td>P trend</td>
<td>0.10</td>
<td>0.10</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Continuous (log scale; per SD)</td>
<td>1.31 (0.95 to 1.81) 0.10</td>
<td>1.31 (0.94 to 1.81) 0.11</td>
<td>1.18 (0.83 to 1.66) 0.36</td>
<td>1.09 (0.77 to 1.55) 0.63</td>
</tr>
</tbody>
</table>

lnUACR, natural log of the urinary albumin-to-creatinine ratio; OR, odds ratio; 95% CI, 95% confidence interval; L-FABP/Cr, urinary liver fatty acid binding protein indexed to urinary creatinine; LOD, limit of detection; KIM-1/Cr, urinary kidney injury molecule 1 indexed to creatinine; Q, quartile; NAG/Cr, urinary N-acetyl-b-D-glucosaminidase indexed to creatinine; NGAL/Cr, urinary neutrophil gelatinase–associated lipocalin indexed to creatinine.

<sup>a</sup>Matching factors incorporated into conditional logistic regression model with no additional covariates.
Table 4. Odds ratios and 95% confidence intervals for incident ESRD for urinary biomarkers modeled categorically and continuously not indexed to urinary creatinine (n=321)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted*</th>
<th>Adjusted for Age</th>
<th>Adjusted for Age and eGFR</th>
<th>Adjusted for Age, eGFR, and lnUACR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>L-FABP (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable (0)</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&gt;0 to &lt;2.4</td>
<td>0.75 (0.36 to 1.56)</td>
<td>0.43</td>
<td>0.75 (0.36 to 1.56)</td>
<td>0.44</td>
</tr>
<tr>
<td>≥2.4 to &lt;7.62</td>
<td>1.03 (0.50 to 2.09)</td>
<td>0.94</td>
<td>1.03 (0.50 to 2.09)</td>
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<tr>
<td>≥7.62</td>
<td>2.04 (0.88 to 4.73)</td>
<td>0.10</td>
<td>2.06 (0.89 to 4.77)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIM-1 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤354.45</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&gt;354.45 to ≤624.42</td>
<td>0.98 (0.50 to 1.91)</td>
<td>0.96</td>
<td>0.99 (0.51 to 1.92)</td>
<td>0.97</td>
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<tr>
<td>&gt;624.42 to ≤1363.16</td>
<td>1.33 (0.68 to 2.61)</td>
<td>0.41</td>
<td>1.33 (0.68 to 2.60)</td>
<td>0.41</td>
</tr>
<tr>
<td>≥1363.16</td>
<td>1.22 (0.61 to 2.44)</td>
<td>0.58</td>
<td>1.21 (0.60 to 2.43)</td>
<td>0.60</td>
</tr>
<tr>
<td>P trend</td>
<td>0.43</td>
<td></td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td>Continuous (log scale; per SD)</td>
<td>1.10 (0.85 to 1.41)</td>
<td>0.47</td>
<td>1.09 (0.85 to 1.41)</td>
<td>0.48</td>
</tr>
<tr>
<td>NAG (milliunits/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.19</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
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<tr>
<td>&gt;2.19 to ≤3.96</td>
<td>1.09 (0.53 to 2.24)</td>
<td>0.81</td>
<td>1.09 (0.53 to 2.24)</td>
<td>0.82</td>
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<tr>
<td>&gt;3.96 to ≤6.93</td>
<td>0.75 (0.36 to 1.55)</td>
<td>0.43</td>
<td>0.75 (0.36 to 1.55)</td>
<td>0.44</td>
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<tr>
<td>&gt;6.93</td>
<td>0.90 (0.42 to 1.95)</td>
<td>0.80</td>
<td>0.91 (0.42 to 1.95)</td>
<td>0.80</td>
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<tr>
<td>P trend</td>
<td>0.55</td>
<td></td>
<td>0.56</td>
<td>0.56</td>
</tr>
<tr>
<td>Continuous (log scale; per SD)</td>
<td>0.96 (0.74 to 1.24)</td>
<td>0.77</td>
<td>0.96 (0.74 to 1.24)</td>
<td>0.77</td>
</tr>
<tr>
<td>NGAL (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8.1</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&gt;8.1 to ≤18.9</td>
<td>0.75 (0.37 to 1.51)</td>
<td>0.42</td>
<td>0.75 (0.37 to 1.51)</td>
<td>0.42</td>
</tr>
<tr>
<td>&gt;18.9 to ≤42.2</td>
<td>0.86 (0.42 to 1.75)</td>
<td>0.68</td>
<td>0.86 (0.42 to 1.75)</td>
<td>0.67</td>
</tr>
<tr>
<td>Continuous (log scale; per SD)</td>
<td>1.16 (0.85 to 1.59)</td>
<td>0.34</td>
<td>1.16 (0.85 to 1.59)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

lnUACR, natural log of the urinary albumin-to-creatinine ratio; OR, odds ratio; 95% CI, 95% confidence interval; L-FABP, urinary liver fatty acid binding protein; KIM-1/Cr, urinary kidney injury molecule 1; NAG, urinary N-acetyl-β-D-glucosaminidase; NGAL, urinary neutrophil gelatinase–associated lipocalin.

*Matching factors incorporated into conditional logistic regression model with no additional covariates.

In UACR, natural log of the urinary albumin-to-creatinine ratio; OR, odds ratio; 95% CI, 95% confidence interval; L-FABP, urinary liver fatty acid binding protein; KIM-1/Cr, urinary kidney injury molecule 1; NAG, urinary N-acetyl-β-D-glucosaminidase; NGAL, urinary neutrophil gelatinase–associated lipocalin.

*Matching factors incorporated into conditional logistic regression model with no additional covariates.
Centrifugation. KIM-1, NGAL, NAG, and L-FABP have been used previously in the ARIC Study to identify markers of tubular injury biomarkers and incident ESRD after accounting for baseline kidney function. At present, studies conducted by our Consortium of urinary tubular injury biomarkers do not suggest that there are consistent, independent associations of these biomarkers with CKD progression. Additional studies are needed to determine if there are subpopulations in which these biomarkers may be of utility.

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Abbott Laboratories had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosures

J.V.B. is a coinventor on kidney injury molecule 1 patents, which have been licensed by Partners Healthcare to a number of companies, and has received royalty income from Partners Healthcare. K.D.L. had reagents donated for previous biomarker studies by Abbott and CMIC.

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