Kidney Medicine

Plasma Biomarkers and Incident CKD Among Individuals Without Diabetes

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Rationale & Objective: Biomarkers of kidney disease progression have been identified in individuals with diabetes and underlying chronic kidney disease (CKD). Whether or not these markers are associated with the development of CKD in a general population without diabetes or CKD is not well established.

Study Design: Prospective observational cohort.

Setting & Participants: In the Atherosclerosis Risk in Communities) study, 948 participants were studied.

Exposures: The baseline plasma biomarkers of kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), soluble urokinase plasminogen activator receptor (suPAR), tumor necrosis factor receptor 1 (TNFR-1), tumor necrosis factor receptor 2 (TNFR-2), and human cartilage glycoprotein-39 (YKL-40) measured in 1996-1998.

Outcome: Incident CKD after 15 years of follow-up defined as ≥40% estimated glomerular filtration rate decline to <60 mL/min/1.73 m^2 or dialysis dependence through United States Renal Data System linkage.

Analytical Approach: Logistic regression and C statistics.

Results: There were 523 cases of incident CKD. Compared with a random sample of 425 controls, there were greater odds of incident CKD per 2-fold higher concentration of KIM-1 (OR, 1.49; 95% CI, 1.25-1.78), suPAR (OR, 2.57; 95% CI, 1.74-3.84), TNFR-1 (OR, 2.20; 95% CI, 1.58-3.09), TNFR-2 (OR, 2.03; 95% CI, 1.37-3.04). After adjustment for all biomarkers, KIM-1 (OR, 1.42; 95% CI, 1.19-1.71), and suPAR (OR, 1.86; 95% CI, 1.18-2.92) remained associated with incident CKD. Compared with traditional risk factors, the addition of all 6 biomarkers improved the C statistic from 0.695-0.731 ($P < 0.01$) and using the observed risk of 12% for incident CKD, the predicted risk gradient changed from 5%-40% (for the 1st–5th quintile) to 4%-44%.

Limitations: Biomarkers and creatinine were measured at one time point.

Conclusions: Higher levels of KIM-1, suPAR, TNFR-1, and TNFR-2 were associated with higher odds of incident CKD among individuals without diabetes.

Visual Abstract included

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Chronic kidney disease (CKD) has been recorded in almost 700 million adults worldwide.[1] In the United States, an estimated 37 million adults have CKD, and 809,000 have kidney failure requiring dialysis.[2,3] Novel therapies have been developed that prevent CKD progression,[4-6] but they may be more effective at preventing kidney failure requiring dialysis or transplant when deployed early.[7-9] Therefore, initiatives focused on the identification of individuals with a high risk of developing CKD are of great importance, as this could allow more targeted prevention and treatment efforts.[10]

Several kidney-specific biomarkers may help with the early identification of high-risk individuals, even when typical kidney parameters such as creatinine, cystatin, and urine albumin still decrease within the normal range.[11] Given the variability of urinary biomarkers related to tonicity and urine flow,[12] we wanted to investigate the utility of plasma biomarkers. In particular, plasma biomarkers related to inflammation and fibrosis (tumor necrosis factor receptor-1 [TNFR-1], tumor necrosis factor receptor-2 [TNFR-2],[13] monocyte chemotactic protein-1 [MCP-1], soluble urokinase-type plasminogen activator receptor [suPAR]),[14] repair (chitinase 3-like protein 1 [YKL-40]),[15] and tubular injury (kidney injury molecule-1 [KIM-1]) have been shown to be associated with progressive CKD in individuals with diabetes, but whether or not this relationship exists with the development of CKD in individuals without diabetes is less clear.[11,16] Among these biomarkers, TNFR-1 and TNFR-2 have been the most studied and consistent in their association with incident and progressive CKD among individuals with and without diabetes.[11-13,16] suPAR, YKL-40, and KIM-1 have also been associated with incident CKD, though less consistently across different study populations.[11,12,16-20] For example, a recent study of individuals without CKD or diabetes in 2 cohorts—the multi-ethnic study of atherosclerosis (MESA) and the reasons for geographic and racial differences in stroke (REGARDS) study—found that TNFR-1 and TNFR-2 were consistently associated with incident CKD. KIM-1, suPAR, and YKL-40 also had significant associations with incident CKD in MESA but not in REGARDS.[11]

PLAIN-LANGUAGE SUMMARY

For people with diabetes or kidney disease, several biomarkers have been shown to be associated with worsening kidney disease. Whether these biomarkers have prognostic significance in people without diabetes or kidney disease is less studied. Using the Atherosclerosis Risk in Communities study, we followed individuals without diabetes or kidney disease for an average of 15 years after biomarker measurement to see if these biomarkers were associated with the development of kidney disease. We found that elevated levels of KIM-1, suPAR, TNFR-1, and TNFR-2 were associated with the development of kidney disease. These biomarkers may help identify individuals who would benefit from interventions to prevent the development of kidney disease.

Our study objective was to assess whether plasma levels of KIM-1, MCP-1, TNFR-1, TNFR-2, suPAR, and YKL-40 were associated with the development of incident CKD above traditional risk factors in individuals without known diabetes in the well curated, longitudinal Atherosclerosis Risk in Communities (ARIC) study.

METHODS

Study Population

The ARIC study is a community-based prospective cohort study designed to evaluate the etiology of cardiovascular disease.[21] Total 15,792 individuals between the age 45-64 years were enrolled in 1987-1989 in 4 communities: Forsyth County, North Carolina; Jackson, Mississippi; northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. All participants provided informed consent at study enrollment and at each follow-up study visit.

Study Design and Outcome

Incident CKD was defined as either a ≥40% estimated glomerular filtration rate (eGFR) decline to a level of <60 mL/min/1.73 m^2 or kidney replacement therapy (dialysis or transplant) at study visit 5 (2011-2013) when compared with study visit 4 (1996-1998, defined as the baseline for this study). Kidney failure or dialysis was determined by linkage with the United States Renal Data System (USRDS) registry.[3] Individuals with albuminuria were included. We excluded individuals with eGFR of <60 mL/min/1.73 m^2, and we excluded individuals with prevalent diabetes defined as self-reported diagnosis of diabetes by a physician, antidiabetic medication, fasting blood glucose ≥ 126 mg/dL, or nonfasting blood glucose ≥ 200 mg/dL at visit 4. We excluded individuals who had missing eGFR at visit 4 or visit 5.

Exposure Variables

We measured concentrations of KIM-1, MCP-1, suPAR, TNFR-1, TNFR-2, and YKL-40[11,20,22-26] in plasma biospecimens collected from study participants at visit 4 (1996—1998) in all cases and a random sample of controls. Biomarkers were measured in duplicate, and the mean of the 2 values was used in the analysis. Samples were stored at −80 °C and analyzed using a multiplex assay on the meso scale discovery platform (Meso Scale Diagnostics) in the CKD Biomarkers Consortium central laboratory at Brigham and Women's Hospital. Samples were repeated if their intra-assay coefficient of variation was >20% for 2 or more analytes, and particularly, KIM-1 (0.74% of samples), MCP-1 (0.11%), suPAR (0.42%), TNFR-1 (2.64%), and TNFR-2 (0.21%) required repeating. The mean coefficients of variation were 5.0% for KIM-1, 2.3% for MCP-1, 4.2% for suPAR, 7.6% for TNFR-1, 2.8% for TNFR-2, and 2.0% for YKL-40. For 47 blind duplicates that were generated at the time of blood specimen collection in the ARIC study, mean coefficients of variation were 12.5% for KIM-1, 9.3% for MCP-1, 9.2% for suPAR, 10.7% for TNFR-1, 6.3% for TNFR-2, and 4.5% for YKL-40.

Covariates

Information on age, sex, race, smoking status, height, weight, blood pressure, health history, and medication use was collected using standardized procedures during visit 4 by trained technicians.[27] Body mass index was calculated using measured height and weight. Blood pressure was measured as the average resting state using 2 measurements with a random zero sphygmomanometer. Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or use of antihypertensive medication. History of congestive heart disease, stroke, or cardiovascular disease was self-reported at visit 1, and for subsequent study visits, cardiovascular events were ascertained through annual telephone interviews, review of hospital records, and active surveillance with events adjudicated by an expert committee.

Urine albumin was measured by a nephelometric method on either the Dade Behring BN100 or the Beckman image nephelometer. Of the entire ARIC cohort 1,065 random individuals were measured on both assays with a mean difference of −53 mg/L for albumin and −0.8 mg/L for urine albumin-to-creatinine ratio (uACR). Plasma and urine creatinine levels were measured by the modified kinetic Jaffé method. Cystatin C was measured using a BN II nephelometer.[28] The eGFR was calculated using the 2021 $eGFR_{Cr\text{-}Cys}$ equation because of its higher accuracy[29] compared with the traditional $eGFR_{Cr}$ equation.[30,31]

Statistical Analysis

Descriptive statistics were used to report baseline participant characteristics in the overall sample and separately for individuals who developed and did not develop CKD. Pearson correlation coefficients were calculated to assess

the intercorrelations among biomarkers and their correlations with eGFR and uACR.

Plasma biomarkers were $\log_2$-transformed to improve the normality of their distribution and to allow for the interpretation of the results at a 2-fold higher biomarker concentration. We additionally analyzed the biomarkers across quartiles, with the lowest quartile being the reference category in individuals who did not develop incident CKD.

We calculated odds ratios (OR)and 95% confidence intervals (CI) for the association between plasma biomarkers and incident CKD using unadjusted logistic regression models. In addition, we used multivariable logistic regression models, adjusted for demographic characteristics (age, sex, and race), study site, health behavior (smoking status), health status (body mass index, systolic blood pressure, anti-hypertensive medication, and history of cardiovascular disease), and log-transformed uACR in model 1; we additionally adjusted for eGFR in a separate model (model 2). To estimate improvement in fit over traditional risk factors, the C statistic was calculated using model 2 with and without the inclusion of individual biomarkers and all 6 biomarkers.

To identify which biomarkers were associated with incident CKD after adjustment for other biomarkers, we constructed a regression model with all 6 biomarkers (KIM-1, MCP-1, suPAR, TNFR-1, TNFR-2, and YKL-40). We used step-wise regression with backward and forwards selection to minimize the Akaike information criterion least absolute shrinkage and selection operator (LASSO) method, and likelihood ratio test to optimize and assess model selection. The LASSO selects variables by penalizing the absolute value of the magnitude of coefficients, and this method selects the most important biomarkers in a rigorous and reproducible way. The coefficients for LASSO regression were then calculated using logistic regression models.

To calculate the improvement in risk prediction with these 6 biomarkers over traditional risk factors, we calculated the individual risk for incident CKD using traditional risk factors with and without the 6 biomarkers. A risk gradient was then calculated by using the 10th and 90th percentile values (ie, the midpoint of the 1st and 5th quintile), with the 50th percentile risk set at the observed risk of incident CKD within the ARIC study from visit 4 to visit 5. We additionally estimated the odds ratio of incident CKD between the 1st and 5th quintiles.

We also performed 2 sensitivity analyses. First, we excluded individuals with baseline albuminuria, defined as >30mg/g, and second, we restricted outcomes to those who met a composite of incident CKD outcomes and progressed to CKD3b+ or kidney failure on dialysis.

Statistically significant results were determined by a 2-tailed $P < 0.05$. Analyses were performed using Stata version 17 statistical software[32] and R Core Team Version 4.2.0[33] with the MASS[34] and ggplot2 package.[35]

RESULTS

Of the 11,656 individuals enrolled in ARIC at visit 4, we excluded 777 for baseline eGFR of <60 mL/min/1.73 m^2 and 1,874 for prevalent diabetes. Of the remaining 9,005 individuals, 5,069 presented for follow-up with eGFR measurements, and the median follow-up time was 14.8 years (25th percentile—75th percentile: 14.2—15.5). We had 609 incident CKD cases, and 86 were excluded for missing covariates. Of the 523 cases, 385 had progressed to CKD3b+ or kidney failure on dialysis or transplant (CKD3b: 269, CKD4: 68, CKD5: 10, and kidney failure requiring dialysis or transplant: 38). Of the 4,030 controls, 425 were then randomly selected for biomarker measurement in addition to the cases.

In the entire cohort at baseline, the mean age was 62 years, 59% were women, and 20% were Black. The mean systolic blood pressure was 127 mm Hg and 39% were taking blood pressure medication. The mean uACR was 14 mg/g, and mean eGFR was 91 mL/min/1.73 m^2 (Table 1). There were 41 incident CKD and 9 nonCKD individuals with baseline uACR > 30 mg/g. See Tables S1, S2, and S3 for study participant characteristics by quartile of biomarkers.

All 6 biomarkers were statistically significant and positively correlated with each other (Table 2). The strongest correlation was observed between TNFR-1 and TNFR-2 ($r = 0.69$). All biomarkers were inversely associated with eGFR, and TNFR-1 and TNFR-2 had the strongest inverse correlations with eGFR (TNFR-1: $r = -0.54$; TNFR-2: $r = -0.51$). All biomarkers were also positively correlated with uACR except for MCP-1.

In unadjusted analyses, higher levels of each of the 6 biomarkers were associated with greater odds of incident CKD (Table 3). Results were similar after adjusting for demographics, CKD risk factors, and uACR. After additional adjustment for baseline eGFR, KIM-1, suPAR, TNFR-1, and TNFR-2 retained statistically significant associations, but associations with MCP-1 and YKL-40 were attenuated and no longer associated with incident CKD (Figure 1). There were statistically significant trends of higher odds of incident CKD across ascending quartiles of KIM-1, suPAR, TNFR-1, and TNFR-2, but not MCP-1 or YKL-40 in model 2 (Figure 2). The strongest associations between biomarkers and incident CKD were observed for KIM-1 (OR for quartile 4 vs quartile 1: 2.32; 95% CI, 1.54-3.49) and suPAR (OR for quartile 4 vs quartile 1: 2.31; 95% CI, 1.48-3.62) (Figure 2). By C statistic, individual KIM-1, suPAR, and TNFR-1 had statistically significant improvements in model prediction of incident CKD beyond traditional covariates (Table 3). Inclusion of all 6 biomarkers together with traditional risk factors also significantly improved model prediction (C statistic 0.732 with a difference of 0.04 and $P < 0.001$).

When all 6 biomarkers were modeled together, KIM-1 (OR, 1.42; 95% CI, 1.19-1.71) and suPAR (OR, 1.86; 95% CI, 1.18-2.92) were statistically significant with greater

Table 1. Baseline Characteristics for the Overall Study Population and According to Incident[a] CKD Status[b]

Characteristic	Overall (N=948)	Incident CKD (n=523)	No CKD (n=425)	P[c]
Age (y)	62 (5)	63 (5)	61 (5)	< 0.001
Female	562 (59.3%)	325 (62.1%)	237 (55.8%)	0.05
Black	189 (19.9%)	118 (22.6%)	71 (16.7%)	0.03
Body mass index (kg/m^2)	29 (5)	29 (6)	29 (5)	0.07
Current smoker	127 (13.4%)	75 (14.3%)	52 (12.2%)	0.34
Systolic blood pressure (mm Hg)	127 (19)	132 (19)	122 (16)	< 0.001
Blood pressure medication use	370 (39%)	243 (46.5%)	127 (29.9%)	< 0.001
History of cardiovascular disease	71 (7.5%)	53 (10.1%)	18 (4.2%)	< 0.001
eGFR (mL/min/1.73 m^2)[d]	91 (92)	89 (90)	93.4 (94)	< 0.001
uACR (mg/g)[e]	4 (2-7)	4 (2-8)	3 (2-6)	< 0.001

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; uACR, urine albumin-to-creatinine ratio.
[a]Incident CKD was defined as either a ≥40% eGFR decline to a level of <60 mL/min/1.73 m^2 or kidney replacement therapy (dialysis or transplant).
[b]Data are reported as number (percent) or mean (standard deviation). No data were missing.
[c]*P*-value from Pearson χ^2 for categorical variables and *t* tests for continuous variables.
[d]2021 CKD-EPI Cr-Cys equation. Data are reported as mean (median).
[e]Data are reported as median (25th percentile—75th percentile).

odds of incident CKD after adjusting for demographic factors, health status, uACR, and eGFR (Table 4). Using LASSO regression, however, both TNFR-1 and TNFR-2 remained in the final model in addition to KIM-1 and suPAR (Table 4), with statistically significant model improvement by the likelihood ratio test (P = 0.04 for inclusion of both TNFR-1 and TNFR-2 with KIM-1 and suPAR).

In terms of risk prediction, the highest quintile vs lowest quintile (with lowest quintile as reference) had significantly increased risk of incident CKD when using traditional risk factors (model 2 without biomarkers; OR 8.19 [95% CI, 5.19-13.17]), and the risk increased further when incorporating the 6 biomarkers (OR 12.77 [95% CI, 7.78-21.57). We then calculated the risk gradient by setting the middle quintile at the 12% observed risk of incident CKD within this cohort over the 15 years of follow-up. The risk gradient for traditional risk factors was 5%-40% (for the first and fifth quintile) and the risk gradient for traditional risk factors with the 6 biomarkers was 4%-44%.

For our sensitivity analyses, the results of the first analysis (exclusion of individuals with uACR > 30 mg/g at baseline) were consistent with the original findings except for unadjusted YKL-40, which was no longer associated with incident CKD. See Table S4. For the second sensitivity analysis, where we restricted the outcome to incident CKD and CDK3b+ or kidney failure on dialysis, all individual biomarker associations were attenuated, but the statistical significance was unchanged compared with the primary analysis (Table S5). In the model with all 6 biomarkers together, however, TNFR-1 was no longer statistically significant, and only the association between both KIM-1 and suPAR with incident CKD remained statistically significant (Tables S5 and S6). In LASSO regression, KIM-1, suPAR, TNFR-1, and TFNR-2 were still selected, but in step-wise regression, only KIM-1 and suPAR remained in the final model.

DISCUSSION

In a population without known diabetes and follow-up after 15 years, we show that higher plasma concentrations of baseline KIM-1, suPAR, TNFR-1, and TNFR-2 were individually associated with higher odds of incident CKD, above and beyond CKD risk factors, baseline eGFR, and albuminuria. These biomarkers may be representative of a subclinical kidney injury process and could help identify individuals at risk of CKD incidence and possible mechanisms of kidney disease pathogenesis. MCP-1 and

Table 2. Pearson Correlation Coefficients for Plasma Biomarkers, eGFR, and uACR

	KIM-1	MCP-1	suPAR	TNFR-1	TNFR-2	YKL-40	eGFR	uACR
KIM-1	1	0.14[a]	0.13[a]	0.24[a]	0.17[a]	0.16[a]	−0.19[a]	0.19[a]
MCP-1	—	1	0.20[a]	0.28[a]	0.25[a]	0.15[a]	−0.20[a]	0.03
suPAR	—	—	1	0.50[a]	0.49[a]	0.14[a]	−0.42[a]	0.12[a]
TNFR-1	—	—	—	1	0.69[a]	0.20[a]	−0.52[a]	0.19[a]
TNFR-2	—	—	—	—	1	0.22[a]	−0.51[a]	0.18[a]
YKL-40	—	—	—	—	—	1	−0.20[a]	0.08[a]

Abbreviations: eGFR, estimated glomerular filtration rate by 2021 Cr-Cys equation; CKD, chronic kidney disease; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; suPAR, soluble urokinase plasminogen activator receptor; TNFR-1, tumor necrosis factor receptor 1; TNFR-2 tumor necrosis factor receptor 2; uACR, urine albumin-to-creatinine ratio; YKL-40, human cartilage glycoprotein-39.
[a]*P* < 0.05.

Table 3. Association of Individual Plasma Biomarkers with Incident[a] CKD in the ARIC Study and Change in C Statistics

Plasma Biomarker	OR (95% CI) for Incident CKD[b]				
	Unadjusted	Model 1[c]	Model 2[d]	C Statistic (95% CI)[e]	ΔC-Statistic
KIM-1	1.66 (1.41-1.95)	1.53 (1.28-1.82)	1.49 (1.25-1.78)	0.711 (0.679-0.744)	0.016[f]
MCP-1	1.36 (1.01-1.82)	1.44 (1.03-2.01)	1.34 (0.96-1.89)	0.697 (0.664-0.730)	0.002
suPAR	2.99 (2.17-4.12)	2.75 (1.90-3.98)	2.57 (1.74-3.84)	0.714 (0.679-0.746)	0.018[f]
TNFR-1	2.13 (1.65-2.74)	2.24 (1.66-3.00)	2.20 (1.58-3.09)	0.713 (0.681-0.745)	0.018[f]
TNFR-2	2.42 (1.76-3.32)	2.21 (1.55-3.15)	2.03 (1.37-3.04)	0.706 (0.673-0.738)	0.010
YKL-40	1.14 (1.01-1.29)	1.04 (0.91-1.18)	1.01 (0.89-1.16)	0.695 (0.662-0.728)	0.000

[a]Incident CKD was defined as either a ≥40% eGFR decline to a level of <60 mL/min/1.73 m^2 or kidney replacement therapy (dialysis or transplant).
[b]OR is calculated per 2-fold higher biomarker level.
[c]Model 1 was adjusted for age, sex, race, study site, body mass index, systolic blood pressure, anti-hypertensive medication use, smoking status, history of cardiovascular disease, and urine albumin-to-creatinine ratio.
[d]Model 2 was adjusted for covariates in model 1 with additional adjustment for $eGFR_{Cr\text{-}Cys}$.
[e]C statistic calculated from Model 2 without any biomarkers was 0.695 (0.662-0.728).
[f]$P < 0.05$ for comparison of C statistic before and after inclusion in Model 2.

YKL-40 were not associated with greater odds of incident CKD. In this study, suPAR was associated with the highest odds of incident CKD, with TNFR-1 and TNFR-2 conferring almost similarly high odds. When all 6 biomarkers were modeled together, only KIM-1 and suPAR were statistically significant across sensitivity analyses and regression models (multivariable, LASSO, and stepwise).

Previous studies have found each of these biomarkers to be associated with CKD progression in individuals with diabetes,[16] but few have specifically looked in individuals without diabetes or CKD at baseline. Other previous studies have been limited to children with CKD,[17] adults with CKD or diabetes,[13,16,18,20,24-26,36] urinary samples (KIM-1, MCP-1, and YKL-40),[37,38] or assessment of individual biomarkers.[20,39,40] By studying this specific population, the CKD Biomarkers Consortium aimed to identify biomarkers strongly associated with incident CKD and, as a consequence, potentially identify individuals who may benefit from interventions to delay the onset of kidney disease.

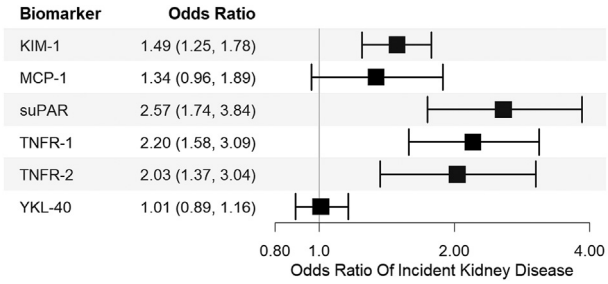

Figure 1. Odds ratio for incident chronic kidney disease per 2-fold higher concentration of each individual plasma biomarker[a]. KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; suPAR, soluble urokinase plasminogen activator receptor; TNFR-1, tumor necrosis factor receptor 1; TNFR-2 tumor necrosis factor receptor 2; YKL-40, human cartilage glycoprotein-39. [a]Logistic regression models were adjusted for age, sex, race, study site, body mass index, systolic blood pressure, anti-hypertensive therapy, smoking status, history of cardiovascular disease, log-transformed urine albumin-to-creatinine ratio, and eGFR.

The CKD Biomarkers Consortium previously studied these same biomarkers in individuals without diabetes or CKD in both MESA and REGARDS using a case-cohort design, and we found that TNFR-1 and TNFR-2 were associated with incident CKD, whereas MCP-1 had no associations. By contrast, the associations with KIM-1, suPAR, and YKL-40 were inconsistent, as they had statistically significant associations individually in MESA but not in REGARDS.[11] This study evaluates the same biomarkers in a different population while also using the 2021 Cr-CysC eGFR equation, which better estimates kidney function. As in MESA, we found both KIM-1 and suPAR to be associated with incident CKD.[11,20,41] suPAR is an inflammatory molecule that may lead to pathologic podocyte activation,[42,43] and it has previously been shown to be associated with eGFR decline in populations with and without CKD[11,14,20] and those without albuminuria.[44] KIM-1, a marker of acute and chronic proximal tubule injury, can be detected in both blood and urine after kidney injury[25] and has been associated with incident and progressive CKD across individuals with[24,38,45] and without diabetes.[46,47] For both TNFR-1 and TNFR-2, we confirmed previous findings of an association with incident CKD. This is not surprising, as previous research has shown a consistent relationship between incident and progressive CKD in individuals with and without diabetes.[11,13,17,18,24,39,48,49] Elevated TNF receptors likely reflect TNF pathway activation, which has been associated with increased vascular endothelial permeability, glomerular basement membrane thickening, glomerular hypercellularity, apoptosis of endothelial cells, and direct toxicity to kidney cells.[50-52]

We did not find either MCP-1 or YKL-40 to be statistically associated with incident CKD. MCP-1 is a pro-inflammatory biomarker, which recruits monocytes and macrophages, and in urine, it has been frequently associated with poor kidney outcomes across multiple clinical settings, such as diabetes, ADPKD, post-cardiac surgery, and post-kidney transplant across incident and progressive

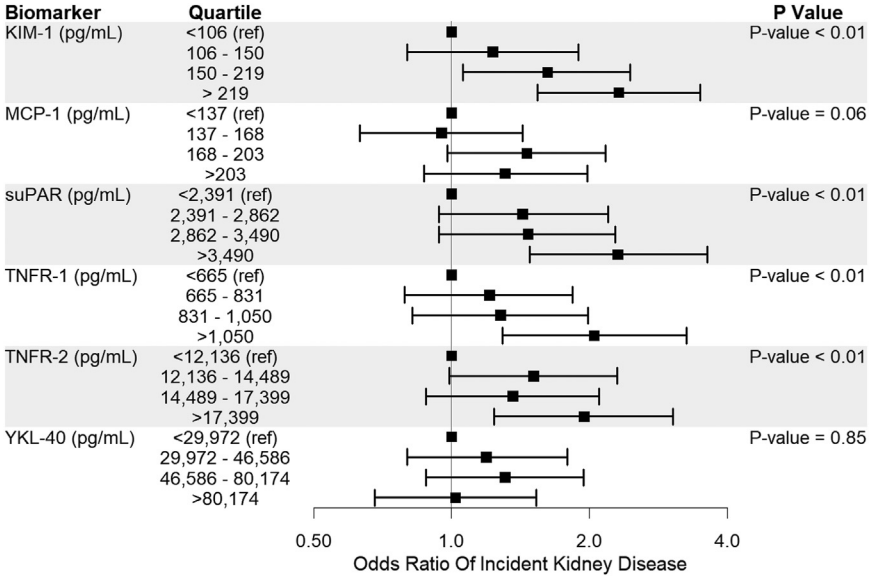

Figure 2. Association of quartiles of plasma biomarkers with incident chronic kidney disease in multivariable logistic regression models in ARIC[a]. KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; suPAR, soluble urokinase plasminogen activator receptor; TNFR-1, tumor necrosis factor receptor 1; TNFR-2 tumor necrosis factor receptor 2; YKL-40, human cartilage glycoprotein-39. [a]Logistic regression model adjusted for age, sex, race, study site, body mass index, systolic blood pressure, anti-hypertensive medication use, smoking status, history of cardiovascular disease, log-transformed urine albumin-to-creatinine ratio, and eGFR. *P*-value from model 2 of individual biomarkers.

CKD.[37,38,53-58] Our null finding with MCP-1 is similar to both MESA and REGARDS.[11] Explanations could include a lack of detectable inflammation or fibrosis in the early kidney disease course versus decreased sensitivity for kidney damage compared with urinary MCP-1.[57] Like REGARDS, but opposite of MESA, we did not see an association with YKL-40; also known as chitinase 3-like 1 (CHI3LI), YKL-40 is thought to regulate the repair phase of acute kidney injury[23] with urinary YKL-40 associated with incident CKD.[37] Notably, YKL-40 has also been shown to be elevated in individuals with cardiovascular disease[59,60] who were included in this study but excluded in MESA.[11] Further studies will be needed to evaluate the utility of MCP-1 and YKL-40 in incident CKD and to assess if urine or plasma is more prognostic of kidney outcomes.

In summary, we present data showing that individual kidney biomarkers, specifically KIM-1, suPAR, TNFR-1, and TNFR-2, were associated with greater odds of incident CKD in people without diabetes. In LASSO regression with all 6 biomarkers, these 4 biomarkers remained in the final model. Although both TNFR-1 and TNFR-2 were no longer statistically significant, this may be because of high collinearity.[61] Notably, inclusion of both TNFR-1 and TNFR-2 improved model fit by the likelihood ratio test. With these findings, there are now multiple studies to tie these biomarkers with incident,[41,62] progressive, and end-

Table 4. Six Biomarker Model for the Association of Plasma Biomarkers with Incident Chronic Kidney Disease

	OR (95% CI) for Incident Chronic Kidney Disease[a]			
Plasma Biomarker	**Model 1[b]**	**Model 2[c]**	**LASSO[d]**	**Stepwise[d]**
KIM-1	1.42 (1.19-1.71)	1.42 (1.19-1.70)	1.40 (1.18-1.68)	1.39 (1.17-1.66)
MCP-1	1.08 (0.76-1.54)	1.08 (0.76-1.54)	—	—
suPAR	1.84 (1.18-2.90)	1.86 (1.18-2.94)	1.95 (1.32-2.90)	2.08 (1.43-3.05)
TNFR-1[e]	1.48 (0.99-2.23)	1.51 (1.00-2.31)	1.39 (0.94-2.06)	1.42 (1.04-1.96)
TNFR-2[e]	1.13 (0.69-1.85)	1.15 (0.70-1.91)	1.13 (0.70-1.83)	—
YKL-40	0.95 (0.83-1.10)	0.95 (0.83-1.10)	—	—

Abbreviations: CI, confidence interval; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; OR, odds ratio; suPAR, soluble urokinase plasminogen activator receptor; TNFR-1, tumor necrosis factor receptor 1; TNFR-2 tumor necrosis factor receptor 2; YKL-40, human cartilage glycoprotein-39.
[a]OR were calculated per 2-fold higher biomarker level.
[b]Model 1 was adjusted for all the biomarkers as well as age, sex, race, study site, body mass index, systolic blood pressure, anti-hypertensive medication use, smoking status, history of cardiovascular disease, urine albumin-to-creatinine ratio, and all 6 biomarkers.
[c]Model 2 was adjusted for covariates in model 1 and eGFR.
[d]Model 2 was used before variable selection through LASSO or Step-wise regression.
[e]Inclusion of both TNFR-1 and TNFR-2 resulted in improved fit by likelihood ratio test ($P < 0.05$) for model 1, model 2, and LASSO.

stage kidney disease[16,18,36,49,63,64] in individuals with and without diabetes, suggesting a pathogenic association. Alternatively, these biomarkers may be strongly associated with kidney outcomes as markers of kidney function despite adjustment for $eGFR_{Cr\text{-}CysC}$. Current applications of these biomarkers for prognostic use could include optimizing selection for clinical trials by both decreasing enrollment size through enrichment for higher-risk participants and identifying individuals who may benefit from targeted preventions for incident CKD, such as increased surveillance or dietary counseling.[8,9,36,65] Although the benefits of biomarker inclusion in addition to traditional risk factors within this study were modest, these results report the potential of kidney-specific biomarkers for risk stratification for incident kidney disease.

This study has multiple strengths. In addition, to being the largest study of these biomarkers and incident CKD to date, the study includes rigorous adjustment of kidney function using the 2021 $eGFR_{Cr\text{-}CysC}$ race-free equation, simultaneous assessment of multiple biomarkers, biomarker measurement in duplicate, and a high level of quality control in a laboratory developed as part of the CKD Biomarkers Consortium. This study has several limitations. Incident CKD was primarily defined using kidney function measured at a study visit and included people who progressed to kidney failure; therefore, the exact timing of progression is unknown during the 15 years of follow-up. This study was restricted to individuals who were alive and completed follow-up at ARIC study visit 5. Survival bias is likely given that death and lost time to follow-up may have disproportionally occurred in those with more severe CKD (and excluded from this study). Biomarkers were only measured at 1 time point, which can lead to measurement errors. Diabetes status was determined by self-report or a single lab measurement, which may have led to misclassification. Results may not be generalizable to the entire US population as individuals were required to complete at least 2 study visits to be included and were restricted to 4 geographic regions within the ARIC study. Finally, given the observational nature, there may still be confounding despite rigorous adjustment for known CKD risk factors. Future studies will need to confirm our results, explore the utility of urinary versus serum biomarkers, and identify which set of biomarkers are most associated with the development of CKD.

In conclusion, baseline KIM-1, suPAR, TNFR-1, and TNFR-2 were associated with incident CKD with ≥40% decline in the eGFR from baseline in individuals without diabetes. These biomarkers may be able to identify individuals who can benefit from early intervention to delay onset of CKD.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Baseline Characteristics of All Individuals By Quartile of sUPAR or KIM-1.

Table S2. Baseline Characteristics of All Individuals By Quartile of TNFRI or TNFRII.

Table S3. Baseline Characteristics of All Individuals By Quartile of MCP-1 or YKL-40.

Table S4. Association of Individual Plasma Biomarkers with Incident Chronic Kidney Disease In Individuals without Albuminuria at Baseline.

Table S5. Sensitivity Analysis of the Association of Individual Plasma Biomarkers with Development of Incident & Advanced Chronic Kidney Disease (CKD3b+ or ESKD).

Table S6. Sensitivity Analysis of the Six Biomarker Model for the Association of Plasma Biomarkers with Incident & Advanced Chronic Kidney Disease (CKD3b+ or ESKD).

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Which kidney biomarkers are associated with development of CKD in adults without diabetes?

Kidney Medicine

Prospective observational cohort Atherosclerosis Risk in Communities (ARIC)

N = 948 adults without diabetes and eGFR ≥ 60

One-time measurement of kidney specific plasma biomarkers

Incident CKD defined as ≥ 40% eGFR decline to < 60 mL/min or dialysis-dependence during follow-up (median: 15 years)

Association of plasma biomarkers with incident CKD*

OR per two-fold higher plasma concentration, 95% CI

	Individual biomarker model	All six biomarkers model
KIM-1	**1.49** (1.25, 1.78)	**1.42** (1.19, 1.70)
MCP-1	**1.34** (0.96, 1.89)	**1.08** (0.76, 1.54)
suPAR	**2.57** (1.74, 3.84)	**1.86** (1.18, 2.94)
TNFR-1	**2.20** (1.58, 3.09)	**1.51** (1.00, 2.31)
TNFR-2	**2.03** (1.37, 3.04)	**1.15** (0.70, 1.91)
YKL-40	**1.01** (0.89, 1.16)	**0.95** (0.83, 1.10)

KIM-1 kidney injury molecule 1, **MCP-1** monocyte chemotactic protein-1, **suPAR** soluble urokinase-type plasminogen activator receptor, **TNFR** tumor necrosis factor receptor, **YKL-40** human cartilage glycoprotein-39.

*Adjusted for age, sex, race, study site, health status, smoking status, UACR, eGFR.

Conclusion: Higher levels of KIM-1, suPAR, TNFR-1, and TNFR-2 are associated with higher odds of incident CKD among individuals without diabetes.

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