Associations of Baseline and Longitudinal Serum Uromodulin With Kidney Failure and Mortality: Results From the African American Study of Kidney Disease and Hypertension (AASK) Trial

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Rationale & Objective: Uromodulin (UMOD) is the most abundant protein found in urine and has emerged as a promising biomarker of tubule health. Circulating UMOD is also detectable, but at lower levels. We evaluated whether serum UMOD levels were associated with the risks of incident kidney failure with replacement therapy (KFRT) and mortality.

Study Design: Prospective cohort.

Setting & Participants: Participants in AASK (the African American Study of Kidney Disease and Hypertension) with available stored serum samples from the 0-, 12-, and 24-month visits for biomarker measurement.

Predictors: Baseline log-transformed UMOD and change in UMOD over 2 years.

Outcomes: KFRT and mortality.

Analytical Approach: Cox proportional hazards and mixed-effects models.

Results: Among 500 participants with baseline serum UMOD levels (mean age, 54 y; 37% female), 161 KFRT events occurred during a median of 8.5 years. After adjusting for baseline demographic factors, clinical factors, glomerular filtration rate, log-transformed urine protein-creatinine ratio, and randomized treatment groups, a 50% lower baseline UMOD level was independently associated with a 35% higher risk of KFRT (adjusted HR, 1.35; 95% CI, 1.07-1.70). For annual UMOD change, each 1–standard deviation lower change was associated with a 67% higher risk of KFRT (adjusted HR, 1.67; 95% CI, 1.41-1.99). Baseline UMOD and UMOD change were not associated with mortality. UMOD levels declined more steeply for metoprolol versus ramipril ($P < 0.001$) as well as for intensive versus standard blood pressure goals ($P = 0.002$).

Limitations: Small sample size and limited generalizability.

Conclusions: Lower UMOD levels at baseline and steeper declines in UMOD over time were associated with a higher risk of subsequent KFRT in a cohort of African American adults with chronic kidney disease and hypertension.

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Uromodulin (UMOD), also known as Tamm-Horsfall protein, is the most abundant protein found in urine. Produced by healthy kidney tubular epithelial cells in the thick ascending limb and early distal convoluted tubule, UMOD is thought to protect against the development of urinary tract infections and kidney stones, play a role in salt-sensitive hypertension, and modulate innate immunity pathways.[1] Although UMOD is expressed primarily at the apical membrane, a few studies have demonstrated some localization of UMOD to the basal plasma membrane, where it is released into circulation, albeit at markedly lower levels than in urine.[2-4] As such, serum UMOD is undetectable in anephric patients, present at low levels among patients with kidney failure treated with dialysis, and increases in patients after receiving a kidney transplant.[1,5] Given its unique specificity to the kidneys, UMOD has therefore emerged as a promising biomarker of kidney tubular health.

To date, most observational studies have suggested that higher serum UMOD levels are associated with improved kidney outcomes. Among individuals with type 1 diabetes, a higher baseline concentration of UMOD was independently associated with lower odds of incident chronic kidney disease (CKD), albuminuria, and rapid decline in estimated glomerular filtration rate (eGFR).[6] Among German and Chinese patients with established CKD and older adults from a United States community-based cohort study, higher baseline circulating levels of UMOD were associated with a markedly lower risk of progression to kidney failure with replacement therapy (KFRT).[7-9] Among kidney transplant recipients, those with higher UMOD concentrations had a lower risk of experiencing kidney allograft failure.[10] In each of these studies, UMOD was measured at only one time point (ie, baseline), and Black individuals were underrepresented.

Using stored serum samples from the AASK (African American Study of Kidney Disease and Hypertension), we investigated whether baseline and longitudinal changes in serum UMOD concentrations were associated with KFRT and mortality risk among self-identified African American adults with CKD attributed to hypertension. We also assessed the effects of randomized

PLAIN-LANGUAGE SUMMARY

Prior studies of uromodulin (UMOD), the most abundant protein in urine, and kidney disease have focused primarily on urinary UMOD levels. The present study evaluated associations of serum UMOD levels with the risks of kidney failure with replacement therapy (KFRT) and mortality in a cohort of African American adults with hypertension and chronic kidney disease. It found that participants with lower levels of UMOD at baseline were more likely to experience KFRT even after accounting for baseline kidney measures. Similarly, participants who experienced steeper annual declines in UMOD also had a heightened risk of kidney failure. Neither baseline nor annual change in UMOD was associated with mortality. Serum UMOD is a promising biomarker of kidney health.

treatment groups (ie, blood pressure goal and drug) on UMOD slope.

Methods

Study Population

The study population consisted of AASK trial participants with available stored serum samples for biomarker measurement (Fig S1). During the trial phase (enrollment from February 1995 through September 1998), 1,094 self-identified African American adults with CKD (GFR, 20-65 mL/min/1.73 m^2) and hypertension (diastolic blood pressure >95 mm Hg) were randomized to a blood pressure goal (mean arterial pressure ≤92 mm Hg or 102-107 mm Hg) and a blood pressure drug (ramipril, metoprolol, or amlodipine).[11] The trial phase was followed by a cohort phase during which 691 participants in whom KFRT had not yet developed were targeted to a blood pressure goal of <140/90 mm Hg (after 2004, <130/80 mm Hg) and received ramipril therapy.[12] Approval for both phases was obtained from the institutional review boards at each study site, and participants provided informed consent. Exclusion criteria have previously been described and included a history of diabetes mellitus and a urine protein-creatinine ratio (UPCR) >2.5 g/g.[11,12]

Biomarker Measurements

The Meso Scale Discovery Platform (Meso Scale Diagnostics) was used to measure UMOD levels from serum samples collected at the 0-, 12-, and 24-month visits of the trial. These immunoassay-based measurements were performed in July 2021. The interassay coefficient of variation, determined from 6% duplicate samples, was 4.2%.

Outcomes and Other Measurements

The primary outcome of interest was incident KFRT (ie, dialysis initiation or kidney transplant).[11,12] We also considered all-cause mortality as a secondary outcome. Blood pressure was measured by trained personnel using a Hawksley random zero sphygmomanometer after ≥5 minutes of rest in a seated position, and taking the average of the last 2 readings. GFR was measured by iodine 125 iothalamate clearance.[11] Twenty-four-hour urine samples were collected, and UPCR was measured at a central laboratory via the pyrogallol red method (for protein) and modified Jaffe reaction (for creatinine).[13-15]

Statistical Analyses

We compared baseline characteristics by tertiles of (1) baseline UMOD levels and (2) UMOD slope using analysis of variance, Kruskal-Wallis test, and Pearson's χ^2 test. UMOD levels were log base-2 ($\log_2$) transformed to achieve a more normal distribution. Kernel density plots were used to visually compare distributions of UMOD level and slope by outcome of KFRT. In our main analyses, we investigated whether baseline UMOD was associated with incident KFRT among 500 AASK trial participants with available measurements at the 0-month visit. Participants were followed until the development of KFRT, death, loss to follow-up, or administrative censoring, whichever came first. The following Cox proportional hazards models were constructed: (1) unadjusted; (2) adjusted for baseline age, sex, systolic blood pressure, body mass index, and current smoking; (3) further adjusted for baseline GFR; (4) further adjusted for baseline $\log_2$(UPCR); and (5) further adjusted for randomized treatment groups (ie, blood pressure goal and blood pressure drug). These analyses were repeated with all-cause mortality as a secondary outcome. There were no missing data for any of the covariates.

A total of 435 participants had UMOD measurements at the 0-month visit plus one additional visit (at 12 mo, 24 mo, or both). More specifically, 324 participants had samples at all 3 visits, 71 had samples at 0 and 12 months only, and 40 had samples at 0 and 24 months only. Annual slopes of $\log_2$(UMOD) were estimated using linear mixed-effects models, allowing for random intercepts and random slopes. We then evaluated whether UMOD slope was associated with the risk of incident KFRT or mortality. For these analyses, the start of follow-up was the 24-month visit. We therefore excluded 17 participants who experienced KFRT or died before this time point, leaving a study population of 418 participants. The 17 participants who were excluded had a lower median UMOD concentration, lower mean GFR, and higher UPCR at baseline compared with the 418 participants who were included. The following Cox proportional hazards models were constructed: (1) unadjusted; (2) adjusted for baseline (0-mo visit) $\log_2$(biomarker); (3) further adjusted for baseline age, sex, systolic blood pressure, body mass index, and current smoking; (4) further adjusted for baseline GFR; (5) further adjusted for baseline $\log_2$(UPCR); and (6) further adjusted for randomized treatment groups. For ease of comparison across variables, we scaled the UMOD slope and baseline UMOD level to a per–standard deviation change.

We used mixed-effects models with random intercept and slope and unstructured covariance matrices to assess whether randomized treatment groups were associated with changes in UMOD levels. For these analyses, the study population consisted of 435 participants with available biomarker slopes, with follow-up beginning at the 0-month visit. We adjusted for baseline age, sex, systolic blood pressure, body mass index, current smoking, GFR, $\log_2$(UPCR), and randomized treatment groups, allowing UMOD slope to vary by each of these variables.

In supplemental analyses, we compared baseline UMOD levels as measured by immunoassays, which we considered to be the gold standard, versus aptamer-based assays, which are increasingly used in biomarker analyses. Aptamer-based measurements of UMOD were performed at baseline (ie, 0-mo visit of the trial) using the SomaScan v.4.1 platform (SomaLogic) in January 2021.[16] SomaScan is an aptamer-based assay that employs single-stranded DNA sequences that have been modified to bind target proteins with high affinities.[17] The interassay coefficient of variation of the SomaScan measures was 3.20%. We assessed correlations between immunoassays and aptamer-based assays as well as their correlations with GFR and $\log_2$(UPCR). We also constructed scatter plots and Bland-Altman plots. Analyses were performed using Stata 15.1 software (StataCorp LLC).

Results

Baseline Characteristics

Among 500 participants with available baseline UMOD levels, the mean age was 54 years, 37% were female, mean

Table 1. Baseline Characteristics of Study Population by Tertiles of Baseline UMOD Levels and UMOD Slope

Characteristic	Tertile 1	Tertile 2	Tertile 3	*P* Value
Baseline UMOD[a]				
Median, pg/mL	9,801 (8,033-11,581)	17,843 (15,618-20,269)	32,328 (25,461-39,034)	–
Range, pg/mL	2,714-13,586	13,599-22,674	22,733-84,997	–
Age, y	53 ± 11	53 ± 11	57 ± 10	0.001
Female sex	52 (31%)	69 (41%)	66 (40%)	0.1
SBP, mm Hg	152 ± 24	150 ± 26	152 ± 23	0.6
Body mass index, kg/m^2	31.1 ± 6.7	31.7 ± 6.3	29.7 ± 6.5	0.01
Current smoking	53 (32%)	46 (28%)	33 (20%)	0.05
GFR, mL/min/1.73 m^2	36.0 ± 11.6	46.3 ± 11.5	51.9 ± 9.6	<0.001
UPCR, g/g	0.27 (0.08-0.76)	0.09 (0.03-0.35)	0.04 (0.02-0.11)	<0.001
Blood pressure goal				0.09
MAP ≤92 mm Hg	75 (45%)	81 (49%)	94 (57%)	
MAP 102-107 mm Hg	92 (55%)	86 (51%)	72 (43%)	
Blood pressure drug				0.9
Ramipril	63 (38%)	62 (37%)	70 (42%)	
Metoprolol	70 (42%)	72 (43%)	64 (39%)	
Amlodipine	34 (20%)	33 (20%)	32 (19%)	
UMOD Slope[b]				
Median, % change per year	−15.1 (−18.4 to −12.4)	−7.4 (−8.6 to −5.8)	−0.9 (−2.8 to 2.0)	–
Range, % change per year	−46.7 to −10.2	−10.2 to −4.2	−4.2 to 13.4	–
Age, y	51 ± 11	55 ± 10	56 ± 11	<0.001
Female sex	55 (39%)	52 (37%)	53 (38%)	0.9
SBP, mm Hg	154 ± 24	153 ± 25	146 ± 24	0.01
Body mass index, kg/m^2	31.5 ± 6.8	30.9 ± 6.8	30.6 ± 6.0	0.6
Current smoking	38 (27%)	37 (27%)	31 (22%)	0.6
GFR, mL/min/1.73 m^2	41.3 ± 12.1	46.0 ± 12.2	49.4 ± 11.2	<0.001
UPCR, g/g	0.28 (0.08-0.82)	0.07 (0.03-0.23)	0.04 (0.02-0.13)	<0.001
$\log_2$(UMOD) at 0 mo	13.8 ± 0.8	14.1 ± 0.8	14.4 ± 0.8	<0.001
Blood pressure goal				
MAP ≤92 mm Hg	82 (59%)	67 (48%)	62 (45%)	0.05
MAP 102-107 mm Hg	58 (41%)	72 (52%)	77 (55%)	
Blood pressure drug				
Ramipril	42 (30%)	55 (40%)	66 (47%)	0.004
Metoprolol	73 (52%)	60 (43%)	41 (29%)	
Amlodipine	25 (18%)	24 (17%)	32 (23%)	

Data presented as median (IQR), mean ± standard deviation, or number (%). There were no missing data. Abbreviations: GFR, glomerular filtration rate; MAP, mean arterial pressure; SBP, systolic blood pressure; UMOD, uromodulin; UPCR, urine protein-creatinine ratio.
[a]Tertile 1, n = 167; tertile 2, n = 167; tertile 3, n = 166.
[b]Tertile 1, n = 140; tertile 2, n = 139; tertile 3, n = 139.

GFR was 45 mL/min/1.73 m^2, and median UPCR was 0.09 g/g. Participants in the highest tertile of baseline UMOD were older and less likely to smoke, and had lower mean body mass index, higher mean GFR, and lower median UPCR (Table 1). Participants who experienced KFRT generally had lower baseline UMOD levels than those who did not (Fig 1).

Among 418 participants with more than one UMOD measurement and without KFRT or death by 24 months, the median change in UMOD was −7.4% per year, with the majority (87%) having a slope that declined. Participants in the highest tertile of UMOD slope (ie, stable to increasing levels) were older, had lower mean systolic blood pressure, higher mean GFR and baseline UMOD levels, and lower median UPCR than participants in lower tertiles (Table 1). Those in the highest tertile were also more likely to be randomized to the ramipril group and less likely to be randomized to the metoprolol group. The distribution of UMOD slope was shifted leftward (ie, decreasing levels) for participants who experienced KFRT compared with those who did not (Fig 1).

Associations of Baseline UMOD With KFRT and Mortality

During a median follow-up of 8.5 years, there were 161 KFRT events. Participants in lower tertiles of UMOD were more likely to experience KFRT (Fig 2). A 50% lower baseline UMOD level was associated with a 2.7-fold higher risk of developing KFRT (unadjusted model: 95% confidence interval [CI], 2.25-3.29; Table 2). Upon further adjustment for baseline sociodemographic and clinical factors and kidney measures, this was attenuated to a 1.4-fold higher risk but remained statistically significant (95% CI, 1.10-1.74). Additional adjustment for randomized treatment groups had minimal impact on risk estimates (HR, 1.35; 95% CI, 1.07-1.70).

During a median follow-up of 9.6 years, 113 participants died. A 50% lower baseline UMOD level was associated with 32% and 40% higher risks of death in the unadjusted model (95% CI, 1.07-1.64; Table 2) and after adjusting for sociodemographic and clinical factors (95% CI, 1.13-1.74), respectively. However, the association lost statistical significance upon additional adjustment for baseline GFR (HR, 1.26; 95% CI, 0.97-1.64).

Associations of UMOD Slope With KFRT and Mortality

In analyses evaluating the association of UMOD slope with KFRT, there were 129 events during a median follow-up of 7.0 years. Participants with the steepest UMOD decline (ie, lowest tertile) were more likely to experience KFRT (Fig 2). In the fully adjusted model, each 1–standard deviation lower UMOD slope was associated with a 67% higher risk of KFRT (95% CI, 1.41-1.99; Table 3). When considering mortality as a secondary outcome, there were 86 deaths during a median follow-up of 7.9 years, and there was no association between UMOD slope and mortality in any of the models (Table 3).

Participants randomized to the intensive blood pressure goal had a steeper decrease in UMOD levels than participants randomized to the standard blood pressure goal ($P = 0.002$), as did participants randomized to receive metoprolol versus those who received ramipril ($P < 0.001$; Table 4). There was no significant difference in change in UMOD levels between participants randomized to receive amlodipine versus metoprolol ($P = 0.08$).

Immunoassay Versus SomaScan Measurements of UMOD

A scatter plot and a Bland-Altman plot of immunoassay versus SomaScan measurements of UMOD are presented in Fig S2. The two methods of measurement were poorly correlated, with Pearson (r) and Spearman (r_s) correlation

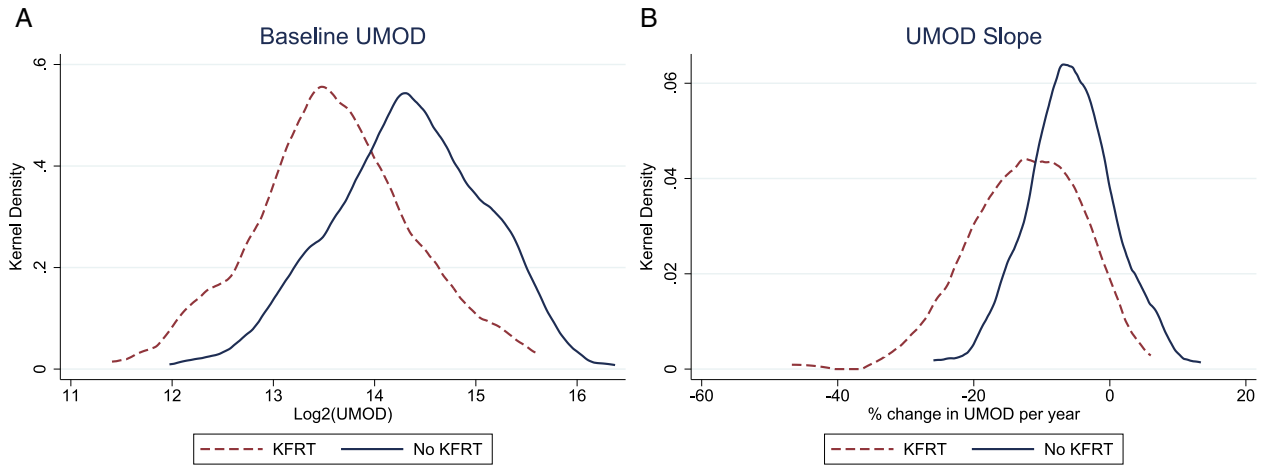

Figure 1. Kernel density plots of baseline uromodulin and uromodulin slope by outcome of kidney failure with replacement therapy. KFRT, kidney failure with replacement therapy; UMOD, uromodulin.

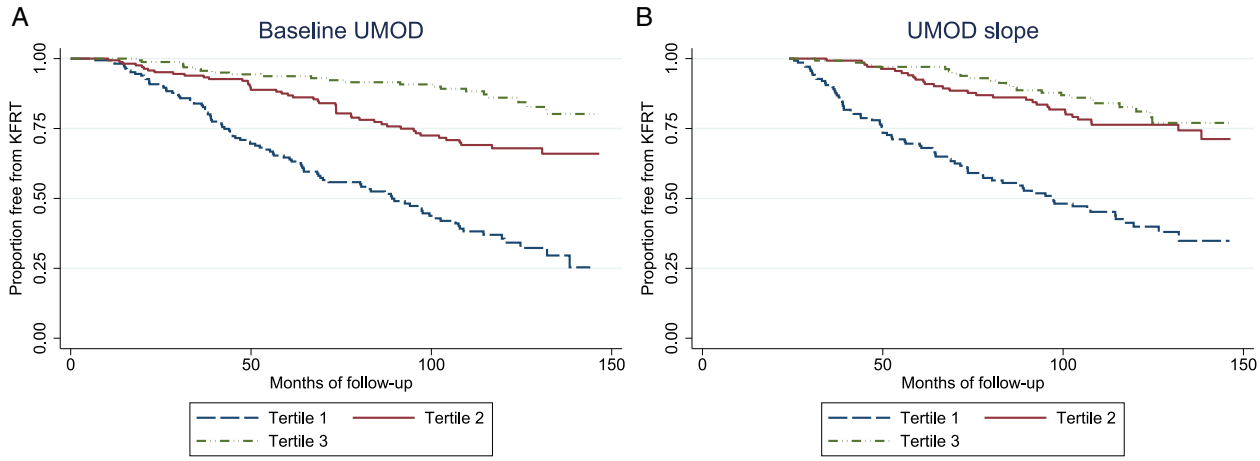

Figure 2. Kaplan-Meier curves of baseline uromodulin and uromodulin slope tertiles with kidney failure with replacement therapy. KFRT, kidney failure with replacement therapy; UMOD, uromodulin.

coefficients of 0.002 and 0.03, respectively. GFR was more strongly correlated with UMOD when measured by immunoassay ($r = 0.48$) than by SomaScan ($r = -0.02$). Similarly, correlations of UMOD with $\log_2$(UPCR) were moderate when measured by immunoassay ($r = -0.37$) and negligible when measured by SomaScan ($r = 0.02$).

Discussion

In this study of African American adults with CKD attributed to hypertension, we report that lower baseline levels of UMOD and steeper declines in UMOD were associated with higher risks of developing KFRT. We also evaluated the effects of the AASK randomized treatment groups on UMOD slope and found that, compared with standard blood pressure control, intensive control conferred greater annual decreases in UMOD, as did metoprolol compared with ramipril. Overall, our results suggest that, among adults with established CKD, having lower levels of UMOD portends worse kidney outcomes.

Table 2. Associations of Baseline UMOD With KFRT and Mortality (N = 500)

Outcome/Model	Baseline UMOD Level (per 50% Lower Baseline Level)	
	HR	95% CI
KFRT		
Unadjusted	2.72	2.25-3.29
+ Age, sex, SBP, BMI, smoking	2.54	2.09-3.09
+ GFR	1.44	1.14-1.81
+ $\log_2$(UPCR)	1.38	1.10-1.74
+ Randomized treatment groups	1.35	1.07-1.70
Mortality		
Unadjusted	1.32	1.07-1.64
+ Age, sex, SBP, BMI, smoking	1.40	1.13-1.74
+ GFR	1.26	0.97-1.64
+ $\log_2$(UPCR)	1.27	0.97-1.67
+ Randomized treatment groups	1.24	0.95-1.63

Abbreviations: BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; KFRT, kidney failure with replacement therapy; SBP, systolic blood pressure; UMOD, uromodulin; UPCR, urine protein-creatinine ratio.

The exclusive production of UMOD by the kidneys makes it an attractive biomarker for study in kidney disease.[1,2] In the urine, UMOD has a propensity to form large polymers that competitively bind to uropathogens and facilitate their clearance from the body. The glycoprotein is also thought to protect against kidney stone formation through its negative charge, which prevents calcium oxalate and calcium phosphate crystals from aggregating in the urine.[1,18]

The role of serum UMOD is less clear. Although older studies linked serum UMOD to inflammation, growing evidence suggests that circulating UMOD may be beneficial by modulating innate immunity pathways.[19,20] More specifically, Micanovic et al described how UMOD deficiency in mice conferred increased bone marrow granulopoiesis with subsequent systemic neutrophilia.[21] In another study, Alesutan et al found that UMOD coimmunoprecipitated with tumor necrosis factor-α and interleukin-1β (proinflammatory cytokines) in human sera from healthy controls and patients undergoing dialysis, suggesting that UMOD may act as a "cytokine trap."[22] In human aortic smooth muscle cells, UMOD appeared to reduce activation of nuclear factor-κB by tumor necrosis factor-α and interleukin-1β.[22] More recently, LaFavers et al reported that, in mouse models of sepsis, the presence of circulating UMOD was associated with better survival. They also demonstrated that UMOD facilitated the clearance of bacteria, likely through the upregulation of mononuclear phagocyte activity.[23] Finally, circulating UMOD may protect against systemic oxidative stress via blockade of TRPM2, a calcium-permeable cation channel

Table 3. Associations of UMOD Slope With KFRT and Mortality (n = 418)

Outcome/Model	UMOD Slope (per 1 SD Lower)		Baseline UMOD Level (per 1 SD Lower)	
	HR[a]	95% CI	HR[a]	95% CI
KFRT				
Unadjusted	2.05	1.80-2.33	–	–
+ Log_2(biomarker)	1.88	1.63-2.16	1.98	1.65-2.39
+ Age, sex, SBP, BMI, smoking	2.06	1.76-2.41	1.92	1.59-2.31
+ GFR	2.00	1.71-2.35	1.36	1.10-1.68
+ Log_2(UPCR)	1.70	1.44-2.01	1.36	1.10-1.68
+ Randomized treatment groups	1.67	1.41-1.99	1.35	1.09-1.68
Mortality				
Unadjusted	1.11	0.91-1.37	–	–
+ Log_2(biomarker)	1.04	0.84-1.30	1.25	1.01-1.56
+ Age, sex, SBP, BMI, smoking	1.02	0.82-1.27	1.37	1.10-1.71
+ GFR	1.01	0.81-1.26	1.28	0.99-1.66
+ Log_2(UPCR)	1.02	0.80-1.28	1.29	0.99-1.67
+ Randomized treatment groups	1.00	0.79-1.28	1.28	0.98-1.66

Abbreviations: BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; KFRT, kidney failure with replacement therapy; SBP, systolic blood pressure; SD, standard deviation; UMOD, uromodulin; UPCR, urine protein-creatinine ratio.
[a]HRs are per 1-SD lower level; SDs are 0.13 for UMOD slope and 0.82 for baseline UMOD level. A lower slope indicates a greater decline in UMOD levels.

that is highly expressed in immune cells. In another study by LaFavers and colleagues, UMOD-knockout mice had higher kidney and serum levels of 8-hydroxy-2′-deoxyguanosine, a biomarker of oxidative damage, than wild-type mice.[3]

UMOD may also affect blood pressure. In mouse models, UMOD augments Na-K-Cl cotransporter activity and renal outer medullary potassium channel expression, increasing sodium retention.[1,24,25] Overexpression of UMOD manifests as salt-sensitive hypertension in mice, whereas UMOD-knockout mice have lower blood pressures and do not develop salt-sensitive hypertension.[1,26,27] The relationship between blood pressure and UMOD may be bidirectional. In a case-control study of the Systolic Blood Pressure Intervention Trial, participants randomized to the intensive group (goal systolic blood pressure <120 mm Hg) had a decrease in urinary UMOD over 1 year compared with the standard group (goal systolic blood pressure <140 mm Hg) among those in whom CKD developed.[28] In the present study, we similarly report that, compared with standard blood pressure control, the intensive blood pressure control arm experienced greater declines in serum UMOD. We note that, in AASK, intensive blood pressure control did not slow CKD progression.[11] The differences in UMOD change may reflect hemodynamic alterations and should be validated in future studies. In contrast, participants randomized to receive ramipril versus metoprolol experienced less serum UMOD declines, and, in the original AASK trial, compared with metoprolol, ramipril was associated with a 22% lower (95% CI, 1%-38%) risk of the clinical composite outcome that included a GFR event, KFRT, or death.[11]

Table 4. Associations of Randomized Treatment Groups With Percent Change in UMOD Levels (n = 435)

Treatment Group	% Change per Year	95% CI
BP goal		
Standard (n = 214)	−8.94	−11.76 to −6.02
Intensive (n = 221)	−13.29	−16.05 to −10.45
BP drug		
Metoprolol (n = 181)	−8.94	−11.76 to −6.02
Ramipril (n = 168)	−2.72	−5.76 to 0.42
Amlodipine (n = 86)	−5.49	−9.27 to −1.55

The predicted percent change in uromodulin was estimated for male nonsmokers with mean values for age, SBP, BMI, GFR, and proteinuria and randomized to the standard BP group and metoprolol unless otherwise noted. Adjustments were made for baseline age, sex, SBP, BMI, smoking, GFR, log_2(UPCR), and randomized group (BP drug for BP goal and vice versa). The percent change was determined by exponentiating β-coefficients as $(2^{\beta} - 1) \times 100$. Abbreviations: BP, blood pressure; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; SBP, systolic blood pressure; UMOD, uromodulin.

Our supplemental work comparing immunoassays versus aptamer-based assays was intended to guide future work and refinement of aptamer-based platforms. Aptamer-based platforms are cost-effective, measuring thousands of proteins simultaneously; however, we and others have previously shown that they are reliable in measuring some but not all proteins.[29] The present study demonstrates that UMOD measurements with immunoassays (the gold standard) and with SomaScan were poorly correlated. Interestingly, there was a bimodal distribution in the SomaScan measurements, but neither mode was correlated with the immunoassay measurements. One potential explanation is that posttranslational modifications of UMOD may differentially affect aptamer versus antibody binding sites on the protein.[29,30] Future versions of the SomaScan platform may close the gap in the accuracy of measurement of this particular protein.

Our study has several strengths. First, we considered baseline UMOD level and UMOD slope. Prior studies of UMOD and kidney outcomes have focused primarily on

the former.[6-10] Second, we adjusted for measured GFR rather than eGFR. In doing so, our findings were less likely to be influenced by inaccuracies in the estimation of baseline kidney measures. Third, we evaluated 2 different approaches to UMOD measurement: the more traditional antibody assay and the newer aptamer-based assay. We also had limitations. First, our sample size was relatively small. Second, the generalizability of our results may be limited because enrollment into AASK was restricted to self-identified African American adults with CKD attributed to hypertension. This could, however, also be viewed as a strength because prior studies of this topic have had an underrepresentation of Black participants.

In summary, lower baseline serum levels of UMOD and steeper declines in UMOD slope were each associated with a higher risk of KFRT among African American adults with CKD attributed to hypertension. Levels of UMOD can be impacted by conventional treatments such as intensive blood pressure control and ramipril therapy. Future studies are needed to further elucidate the mechanisms by which lower serum UMOD levels are associated with worse kidney outcomes.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flow chart of study population.

Figure S2: Scatter plot and Bland-Altman plot of immunoassay versus SomaScan measurements of UMOD.

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