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Association of serum and urinary uromodulin and their correlates in older adults—The Cardiovascular Health Study

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Abstract

Uromodulin is released into serum (sUMOD) and urine (uUMOD) exclusively by renal tubular cells. Both sUMOD and uUMOD are correlated with estimated glomerular filtration rate (eGFR), and associated with mortality and cardiovascular disease (CVD). However, no study to our knowledge has measured both sUMOD and uUMOD in the same population, thus the relationship of sUMOD with uUMOD with one another, and their respective correlates have not been evaluated simultaneously. We evaluated the correlations of sUMOD, uUMOD with eGFR in a random sub-cohort (n = 933) of the Cardiovascular Health Study and their associations with demographic and laboratory parameters and CVD risk factors using multi-variable linear regression analysis. The mean age of the cohort was 78 years, 40% were male and 15% were Black. The mean sUMOD level was 127 ng/mL, uUMOD was 30 500 ng/mL and eGFR was 63 mL/min/1.73 m^2. Correlation between sUMOD and uUMOD, adjusted for eGFR was moderate (r = 0.27 [95% confidence interval = 0.21–0.33]). The correlation of eGFR with sUMOD (r = 0.44 [0.39–0.49]) was stronger

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

SUPPORTING INFORMATION

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than with uUMOD (r = 0.21 [0.15–0.27]). In multi-variable analysis adjusting sUMOD for uUMOD and vice versa, sUMOD was independently associated with eGFR (β = 1.3 [1.1–1.6]), log2 C-reactive protein (β = −4.2 [−6.8 to −1.6]) and male sex (β = −13.6 [−22.7 to −4.5]). In contrast, male sex was associated with higher uUMOD (β = 3700 [400–7000]), while diabetes (β = −6400 [−10 600 to −2100]) and hypertension (−4300 [−7500 to −1100]) were associated with lower uUMOD levels. We conclude that sUMOD is more strongly associated with eGFR compared with uUMOD. Correlates of sUMOD and uUMOD differ substantially, suggesting that apical and basolateral secretion may be differentially regulated.

Keywords

chronic kidney disease; geriatrics; regression; Tamm-Horsfall protein; tubular function; uromodulin

Uromodulin is exclusively expressed in the ascending loop of Henle and distal tubule and then released into both the tubular lumen and the blood, with approximately 100- to 300-fold higher concentrations in the urine.[1] Urinary uromodulin (uUMOD) has been proposed to be protective against nephrolithiasis and urinary tract infections and regulates the tubular salt and water transport.[1] Serum uromodulin (sUMOD) appears to have immunomodulatory functions both locally in the kidney and the circulation.[1–3] sUMOD and uUMOD correlate directly with estimated glomerular filtration rate (eGFR).[4,5] We have shown that lower sUMOD and uUMOD are associated with higher risk for mortality, cardiovascular disease (CVD) and end-stage renal disease.[5–7]

Currently, it is unclear whether blood, urine or both should be used to measure uromodulin as a marker for tubular health. Current measures of kidney function, that is, markers of glomerular filtration do not accurately represent degree of tubular function, injury or atrophy.[8] Due to different physiological functions, we hypothesized that correlates of sUMOD, uUMOD would differ, and their concentrations would vary based on the clinical situation such as inflammation. Understanding correlates of sUMOD and uUMOD would help to better interpret its concentrations as markers of tubular function. In this cross-sectional analysis, we evaluated the inter-correlations of sUMOD and uUMOD, and their respective associations with eGFR and other health-related factors within the Cardiovascular Health Study (CHS).

1 | MATERIAL AND METHODS

1.1 | Study participants and study design

Cardiovascular Health Study is an observational, community-based cohort study that included men and women aged ≥65 years (n = 5888 Medicare eligible participants[9]). All participants provided informed consent, and local institutional review boards approved the study methods. We assayed sUMOD, uUMOD in a random sub-cohort of 933 participants from the 1996–1997 study visit when blood and urine samples were collected on the same day. This sub-sampling strategy reduced the costs for biomarker measurement but represents the overall cohort in terms of clinical and laboratory characteristics.[10]

1.2 | Exposure

Blood and urine samples were stored at −70°C until they were thawed for measurement. Assays were performed using two different commercial enzyme-linked immunosorbent assay (ELISA, UMOD: Euroimmun Medizinische Labordiagnostika AG, Lübeck, Germany; uUMOD: MD Bioproducts, St Paul, Minnesota).[4,5] We chose different assays because the MD Bioproducts assay was no longer available at the time that the serum measurements were performed.

1.3 | Statistical analysis

We characterized the cohort using mean and SD for continuous variables and percentages for binary and categorical variables. We evaluated the correlations of sUMOD and uUMOD with eGFR using Pearson correlation coefficients. We assessed associations with sUMOD and uUMOD, respectively, using nested multi-variable linear regression analysis adjusting for demographics, CVD risk factors, prevalent CVD, inflammatory variables, eGFR and albuminuria. All analyses were conducted using R, version 3.5.1 (R Core Team [2018], Vienna, Austria).

2 | RESULTS

2.1 | Population characteristics

The mean age of the cohort was 78 ± 5 years, 40% were male, 15% were Black and eGFR was 63 ± 19 mL/min/1.73 m^2 (Table 1). Mean sUMOD was 127 ± 64 ng/mL and uUMOD was more than two-orders of magnitude higher (30 500 ± 19 800 ng/mL).

2.2 | Correlations of sUMOD, uUMOD and eGFR

The correlation between sUMOD and uUMOD was 0.33 (95% confidence interval: 0.2–0.38). After adjustment for eGFR, this correlation was attenuated slightly (r = 0.27 [0.21–0.33]). The correlation of sUMOD with eGFR was 0.44 (0.39–0.49) and nominally higher compared to uUMOD (r = 0.21 [0.15–0.27]).

2.3 | Linear regression analysis

In multi-variable regression analysis adjusting for all co-variables, each 1000 ng/mL higher uUMOD was associated with a 0.8 (0.6–1.1) ng/mL higher in sUMOD. Male sex was associated with a 13.6 (−22.7 to −4.5) ng/mL lower sUMOD level (Table 2). Each 2-fold higher C-reactive protein (CRP) was associated with a 4.2 (−22.7 to −4.5) ng/mL lower sUMOD level, while each mL/min/1.73 m^2 higher eGFR was associated with 1.3 (1.1–1.6) ng/mL higher sUMOD. In contrast, albumin/creatinine ratio was not independently associated with either sUMOD or uUMOD. In general, the strengths of association were similar in the univariable and the multi-variable analysis (Table S1).

In contrast to sUMOD, male sex was associated with a 3700 (400–7000) ng/mL higher uUMOD level (Table 2). Furthermore, the presence of diabetes (−6400 [−10 600 to −2100]) and hypertension (−4300 [−7500 to −1100]) were associated with lower uUMOD. sUMOD, diabetes and hypertension were also associated with uUMOD in univariable analysis, but male sex was not (Table S2).

Further nested multi-variable regression models are presented in Tables S1 and S2.

3 | DISCUSSION

To our knowledge, no prior epidemiologic study has simultaneously measured sUMOD and uUMOD, thus their relationship with one another, eGFR and other correlates is largely unknown. We demonstrate that sUMOD and uUMOD concentrations are moderately correlated with one another, that sUMOD was more strongly associated with eGFR, and after mutual adjustment, the relationship of uUMOD with eGFR was rendered no longer statistically significant. The correlates of sUMOD and uUMOD differ substantially, suggesting that factors other than nephron mass impact the secretion of uromodulin into blood and urine.

In addition to the association with eGFR, lower sUMOD concentrations in males have been described previously.[11] Furthermore, an association of sUMOD with CRP, body mass index, systolic blood pressure, triglycerides, fasting glucose, uric acid and cholesterol have been reported.[12] The association with CRP is supported by translational research in animal models demonstrating that sUMOD has an anti-inflammatory effect and regulates oxidative stress both locally in the kidney and systemically.[2,3,13] However, currently it is unknown whether inflammation leads to lower sUMOD levels or vice versa. The cross-sectional design of the present study also precludes evaluating this causal relationship, but we demonstrate that the relationship of sUMOD with CRP remains robust even after accounting for the concentration of UMOD in the urine.

Few studies have evaluated the correlates of uUMOD. Lower eGFR has been shown to be associated with lower uUMOD levels.[5] Although we also observed this association, we found that it was largely attenuated by the simultaneous adjustment for sUMOD. Consistent with our prior study, male sex was positively associated with uUMOD.[14] However, this association became significant only after adjustment for sUMOD, so the relevance of this association remains unclear. A next step toward practical application of UMOD will be to ascertain normal sUMOD and uUMOD values in the healthy population. In line with our results, previous studies have reported lower uUMOD excretion in diabetes and hypertensive patients.[15] It seems likely that these findings may represent tubular damage and a resulting low nephron mass secondary to hypertension or diabetes. However, it remains possible that these findings represent disease specific mechanisms independent of nephron mass. Ideally, future studies would evaluate patients with similar eGFR in a CKD population with distinct kidney pathologies. Last, it is possible that uUMOD glycation in diabetic kidney disease might influence accurate measurement of uUMOD.[16]

Our study has several strengths. To our knowledge, no large study has concurrent measures of sUMOD and uUMOD. Due to multiple variables in nested regression models, we reduced the risk of unmeasured confounding. As the major limitation, we did not use the same assay for measurements of UMOD in blood and urine. However, the assay we used for serum measurements is not validated for urine and the assay we used for urine measurements was not available at the subsequent time when we performed the serum analyses. Furthermore, while it is known that neither freeze-thaw-cycles nor storage at −80°C have a major impact

on uUMOD concentrations,[17] there are no published data on for the effect of storage time or freeze thaw on sUMOD concentrations.

In conclusion, sUMOD is more strongly correlated with eGFR than uUMOD, and sUMOD and uUMOD have unique correlates. This might be due to different physiological roles of uromodulin in the kidney interstitium and systemic circulation as compared to the tubular lumen. If uromodulin were to be used as a marker of tubular function or nephron mass in the future, clinicians and investigators should be aware of conditions affecting sUMOD and uUMOD concentrations and take these associations into account when interpreting sUMOD or uUMOD as markers for tubular function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY AT A GLANCE

Although both serum and urine uromodulin levels are correlated directly with eGFR, it is unclear which is better. In this study, serum uromodulin is more strongly associated with eGFR than urine uromodulin. In addition, correlates of serum and urine uromodulin differ, thus they may be differentially regulated to a certain extent.

TABLE 1

Characteristics of participants in the random sub-cohort (n = 933)

Variable	
Demographics	
Age (y)	78.1 (4.8)
Male	39.7
Race Black	15.3
BMI (kg/m^2)	26.9 (4.7)
Site	
Wake Forest	23.2
UC Davis	28.5
Johns Hopkins	21.8
Pittsburgh	26.6
Laboratory measures	
sUMOD (ng/mL)	127.2 (63.6)
uUMOD (ng/mL)	30 500 (19 800)
CKD (eGFR < 60 mL/min/1.73 m^2)	41.7
eGFR (mL/min/1.73 m^2)	63.4 (18.6)
Albuminuria (ACR > 30 mg/g Cr)	20.5
log2 (ACR) (mg/g)	3.8 (1.9)
Fasting glucose (mg/dL)	107.4 (34.6)
log2 (CRP) (mg/dL)	1.3 (1.6)
Total cholesterol (mg/dL)	201.4 (38.8)
Serum albumin (g/dL)	3.8 (0.3)
CVD risk factors and prevalent CVD	
Systolic BP (mm Hg)	137.0 (21.0)
Diastolic BP (mm Hg)	69.8 (11.0)
Diabetes	25.3
Hypertension	60.0
Heart failure	9.2
Cardiovascular disease	17.5
Medication use	
Lipid lowering	12.0
Antihypertensive	55.4

Note: Continuous variables are presented as mean (SD), categorical variables in percentage of total population. Cardiovascular disease is defined as history of myocardial infarction and/or stroke prior to baseline assessment.

Abbreviations: ACR, albumin/creatinine ratio; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; Cr, creatinine; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; sUMOD, serum uromodulin; uUMOD, urinary uromodulin.

TABLE 2

Multi-variable linear regression analysis

	sUMOD as dependent variable		**uUMOD as dependent variable**	
Co-variable	***β***	**95% CI**	***β***	**95% CI**
Age (y)	0.2	(−0.8, 1.1)	−0.2	(−0.5, 0.2)
Male	**−13.6**	**(−22.7, −4.5)**	**3.7**	**(0.4, 7.0)**
Black race	6.8	(−4.8, 18.4)	−2.2	(−6.4, 2.0)
BMI (kg/m^2)	−0.7	(−1.7, 0.2)	0.2	(−0.2, 0.5)
Diabetes	4.9	(−6.9, 16.8)	**−6.4**	**(−10.6, −2.1)**
Hypertension	−5.8	(−14.7, 3.1)	**−4.3**	**(−7.5, −1.1)**
Prevalent CVD	−3.6	(−14.3, 7.1)	−0.0	(−3.9, 3.8)
Prevalent HF	−13.0	(−27.3, 1.4)	−0.1	(−5.3, 5.1)
Total cholesterol (mg/dL)	0.1	(−0.1, 0.2)	0.0	(−0.0, 0.1)
Serum albumin (g/dL)	−3.0	(−17.6, 11.7)	5.2	(−0.2, 10.4)
Interleukin-6 (pg/mL)	0.0	(−0.1, 0.1)	−0.0	(−0.0, 0.0)
log2 CRP (mg/dL)	**−4.2**	**(−6.8, −1.6)**	0.7	(−0.3, 1.6)
$eGFR_{cys}$ (mL/min/1.73 m^2)	**1.3**	**(1.1, 1.6)**	0.0	(−0.1, 0.1)
log2(ACR) (mg/g creatinine)	−2.0	(−4.3, 0.3)	−0.5	(−1.3, 0.4)
sUMOD (per ng/mL)			**0.1**	**(0.1, 0.1)**
uUMOD (per 1000 ng/mL)	**0.8**	**(0.5,1.0)**		

Note: *β* indicates the amount of difference in serum uromodulin in ng/mL by one unit increase of the covariate. Numbers in bold indicate significant associations; negative coefficients indicate lower levels of the dependent variable, positive coefficients indicate higher levels.

Abbreviations: ACR, urinary albumin/creatinine-ratio; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; uUMOD, urinary uromodulin.