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How to cite

PRUIJM, Menno et al. Associations of Urinary Uromodulin with Clinical Characteristics and Markers of Tubular Function in the General Population. In: Clinical journal of the American Society of Nephrology, 2016, vol. 11, n° 1, p. 70–80. doi: 10.2215/CJN.04230415

This publication URL: https://archive-ouverte.unige.ch/unige:89454

Publication DOI: 10.2215/CJN.04230415

Associations of Urinary Uromodulin with Clinical Characteristics and Markers of Tubular Function in the General Population

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Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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Abstract

Background and objectives Allelic variants in *UMOD*, the gene coding for uromodulin, are associated with rare tubulointerstitial kidney disorders and risk of CKD and hypertension in the general population. The factors associated with uromodulin excretion in the normal population remain largely unknown, and were therefore explored in this study.

Design, setting, participants, & measurements Urinary uromodulin excretion was measured using a validated ELISA in two population-based cohorts that included more than 6500 individuals. The Swiss Kidney Project on Genes in Hypertension study (SKIPOGH) included 817 adults (mean age±SD, 45±17 years) who underwent renal ultrasonography and performed a 24-hour urine collection. The Cohorte Lausannoise study included 5706 adults (mean age, 53±11 years) with fresh spot morning urine samples. We calculated eGFRs using the CKD-Epidemiology Collaboration formula and by 24-hour creatinine clearance.

Results In both studies, positive associations were found between uromodulin and urinary sodium, chloride, and potassium excretion and osmolality. In SKIPOGH, 24-hour uromodulin excretion (median, 41 [interquartile range, 29–57] mg/24 h) was positively associated with kidney length and volume and with creatinine excretion and urine volume. It was negatively associated with age and diabetes. Both spot uromodulin concentration and 24-hour uromodulin excretion were linearly and positively associated (multivariate analyses) with eGFR<90 ml/min per 1.73 m^2.

Conclusion Age, creatinine excretion, diabetes, and urinary volume are independent clinical correlates of urinary uromodulin excretion. The associations of uromodulin excretion with markers of tubular functions and kidney dimensions suggest that it may reflect tubule activity in the general population.

Clin J Am Soc Nephrol 11: 70–80, 2016. doi: 10.2215/CJN.04230415

Introduction

Uromodulin (Tamm–Horsfall protein) is the most abundant protein excreted in normal human urine (1). Uromodulin is exclusively synthesized by the epithelial cells lining the thick ascending limb (TAL) of the loop of Henle, where it is sorted to the apical plasma membrane and released into the tubular lumen by proteolytic cleavage (2). The biologic role of uromodulin is emerging, with studies in knockout mice showing that it regulates NaCl transport processes operating in the TAL (3,4).

The interest in uromodulin was boosted when genetic studies revealed that mutations of the *UMOD* gene, which encodes uromodulin, cause rare inherited forms of tubulointerstitial kidney diseases (5). Furthermore, multiple genome-wide association studies (6,7) and sequencing efforts (8) have identified common single-nucleotide polymorphisms in *UMOD* associated with eGFR and the risk for developing CKD in the general population (1,9). The abundant excretion of uromodulin in physiologic conditions and the fact that it is exclusively produced by TAL cells, which play a major role in sodium and divalent cation handling and in urinary concentrating ability, suggest that it could represent a marker of renal tubular function. Indeed, uromodulin expression has recently been associated with the phosphorylation/activation of Na(+)-K(+)-2Cl(−) cotransporter-2 (NKCC2), renal sodium handling, and BP regulation in mice and humans (10).

Preliminary studies have reported positive associations between urinary uromodulin and eGFR (11–13). However, these studies were limited by their small sample size and variable urine sample processing. The relationships between urinary uromodulin, electrolyte handling, and eGFR need confirmation in larger studies using reliable dosing methods. Similarly, the clinical and biologic determinants of uromodulin excretion remain largely unknown.

In this cross-sectional study, we investigated the clinical and biologic correlates of uromodulin excretion and analyzed the potential associations of urinary uromodulin with markers of glomerular and tubular functions and ultrasonography-assessed kidney dimensions in two large, population-based studies.

Materials and Methods

Study Populations

Urinary uromodulin was measured in two Swiss population-based studies: (*1*) the Swiss Kidney Project on Genes and Hypertension (SKIPOGH) study and (*2*) the Cohorte Lausannoise (CoLaus) study. Each study protocol was approved by local ethical committees. All participants provided written informed consent.

The SKIPOGH study randomly selected individuals from the general population in Bern, Lausanne, and Geneva between 2009 and 2012, as described previously (14). Inclusion criteria were: (*1*) minimum age 18 years, (*2*) European descent, and (*3*) at least one first-degree family member willing to participate. A study visit was performed after an overnight fast and included a questionnaire, a complete physical examination, blood sampling, and 24-hour urine collection. Renal ultrasonography was performed to measure kidney length and volume as an anatomic proxy of absolute renal mass. Creatinine-based eGFR calculated with the CKD-Epidemiology Collaboration (CKD-EPI) equation, cystatin C–based eGFR, and 24-hour urinary creatinine clearance were used as a proxy for glomerular function (15). The 24-hour urinary osmolar excretion (24-hour urinary volume × 24-hour urinary osmolality) and 24-hour urinary excretion of electrolytes (24-hour urinary volume × electrolyte concentration) were also measured.

The CoLaus study is a population-based study (2003–2006) conducted in Lausanne (16). Inclusion criteria included age 35–75 years and being of European descent. All participants attended the outpatient clinic the morning after an overnight fast. The examination included a detailed questionnaire, anthropometric measures, laboratory testing, and a spot morning urine sample.

Technical Measurements

Renal Ultrasonography. In SKIPOGH, renal gray-scale B-mode ultrasonography was performed according to a standardized procedure (see Supplemental Material) (14,17,18).

Laboratory Measurements. Electrolytes, hematology variables, and glycemia were measured in local university laboratories using standard clinical laboratory methods. Creatinine was measured using the Jaffe kinetic compensated method (intra-assay variability, 0.7%–2.9%; Roche Diagnostics). The CKD-EPI formula was used to calculate the eGFR (19). Urine albumin was measured quantitatively by immunonephelometry.

In SKIPOGH, cystatin C was measured using immunonephelometry (Latex Cystatin C Assay; Siemens, Germany). A 24-hour urine collection was obtained; incomplete collections were defined as a volume <300 ml/24 h, a 24-hour urinary creatinine excretion <0.1 mmol/kg body wt, or reported as incomplete by the participant (20). Urine collections containing >0.4 mmol/kg creatinine were also excluded from further analysis (21). In CoLaus, urinary uromodulin, creatinine, electrolytes and osmolality concentrations were measured in morning spot urine samples. All urinary biochemical parameters in the two studies, including uromodulin, were measured from samples stored at −80° C, in the same biochemical platform at the University of Zürich. The 24-hour urinary osmoles excretion in milliosmoles was calculated as 24-hour osmolality×24-hour urinary volume.

Urinary uromodulin concentration was measured by ELISA as described previously (22). Human uromodulin (stock solution 100 μg/ml; Millipore) was used for the standard curve. The uromodulin ELISA has a sensitivity of 2.8 ng/ml, a linearity of 1.0, an interassay variability of 3.3%, and an intra-assay variability of 5.5%. Urinary osmolality was measured using an Advanced Osmometer (Advanced Instruments, Norwood, MA) based on the freezing-point depression. A control (Clinitrol 290) and a set of calibration standards (50, 850, and 2000 mOsm/kg) were used before running of each sample batch. The coefficient of variability was 0.19% in urine.

Statistical Analyses

The continuous variables are expressed as mean±SD when approximately normally distributed and as median and interquartile range otherwise. Categorical variables are expressed as numbers and percentages. Kernel density graphs were used to show uromodulin distribution. Associations between uromodulin and the other variables of interest were then explored using Pearson or Spearman correlations, as appropriate. The linearity of the main associations of interest was tested graphically through scatter plots and statistically using tertiles in multivariable models.

Multivariate linear mixed models were finally used to explore the associations of interest. For the exploration of correlates of uromodulin and its associations with renal function, uromodulin was the dependent (outcome) variable. For the electrolytes and albuminuria analyses, uromodulin was the independent variable. Continuous variables that were not normally distributed were transformed for the purpose of these analyses to better achieve normality of the residuals or homoscedasticity or to better approximate linear relationships. Urinary uromodulin, electrolytes, and osmolar excretion were all square-root transformed.

In SKIPOGH, ultrasonography-assessed renal volume was calculated as 0.523×length×width×transverse diameter (23). All urinary analyses were performed on the basis of 24-hour urinary uromodulin excretion (mg/24 h) and urinary electrolyte excretion (mmol/24 h). In CoLaus, spot morning urinary concentrations of uromodulin and electrolytes were used for analysis. The CoLaus models were adjusted for urinary creatinine concentration (24). In SKIPOGH, a supplementary analysis was performed in which urinary creatinine was added to the model (model 2), for two reasons: to increase the comparability with CoLaus and to take into account the strong association between 24-hour urinary uromodulin and creatinine excretion. All analyses were repeated with exclusion of outlier values (defined as values >99th or <1st percentile). We further explored the association of urinary uromodulin with eGFR

by stratifying eGFR in <90 or ≥90 ml/min per 1.73 m^2 because graphically the relationship between urinary uromodulin and eGFR was not merely linear, with a change in slope at around 90 ml/min per 1.73 m^2; this was confirmed in spline regression with a knot at 90 ml/min per 1.73 m^2. This cutoff was also chosen on the basis of CKD classification.

Statistical analyses were conducted using Stata software, version 11.0 (Stata Corp., College Station, TX). Statistical significance was considered for a two-sided P value <0.05.

Results

Participants and Baseline Characteristics

The SKIPOGH study included a total of 1066 individuals with measurement of urinary uromodulin. Participants with missing or incomplete 24-hour urine collections (n=83), missing (n=12) or insufficient-quality (n=21) ultrasonography data were excluded. Participants with renal cysts (n=133), for which the ultrasonography-based assessment of renal length and volume is less precise, were also excluded, leaving a total of 817 participants for analysis. In the CoLaus study, 6184 individuals were included. Uromodulin dosage was missing for 362 patients, and 116 patients had incomplete demographic or urinary data, leaving 5706 participants for the present analysis. The baseline characteristics of the two study populations are shown in Table 1. Because of differences in the required minimal age for inclusion (18 versus 35 years, respectively), SKIPOGH participants were younger, less often had diabetes or hypertension, and had a higher eGFR compared with CoLaus participants.

Distribution and Correlates of Urinary Uromodulin

The distribution of urinary uromodulin according to sex in the two cohorts is shown in Figure 1. There were no sex differences in uromodulin concentrations or 24-hour urinary uromodulin excretion; therefore, the higher uromodulin-to-creatinine ratios in women were due to lower urinary creatinine values and not due to higher uromodulin values.

Table 2 presents the clinical correlates of 24-hour uromodulin excretion rate (24-hour uromodulin excretion rate in the urine [expressed in mg/day] [24-hour UER]) in SKIPOGH. In univariate and multivariate analyses, age and diabetes were negatively associated with 24-hour UER, whereas urinary volume was positively associated with 24-hour UER. Male sex and body height were positively associated with 24-hour UER in univariate analysis, but not in multivariate analysis (model 1). After adjustment for creatinine excretion, the association between 24-hour UER and age disappeared, but the association for diabetes and 24-hour urine volume persisted. Daily creatinine excretion did not differ between quintiles of 24-hour urine volume, suggesting that the association

Table 1. Baseline characteristics of participants in the two populations

Characteristics	SKIPOGH (n=817)	CoLaus (n=5706)
General characteristics		
Women, %	53	53
Age, yr	45±17	53±11
Body weight, kg	72±14	73±15
Body height, cm	171±9	169±9
BMI, kg/m^2	24.5±4	25.7±5
Hypertension, %	18.8	35.6
Diabetes, %	3.7	6.0
Smoking, %	24.9	26.9
Diuretic use, %	4.1	6.4
Laboratory data		
$eGFR_{creatinine}$, ml/min per 1.73 m^2	98±17	86±15
$eGFR_{cystatin\ C}$, ml/min per 1.73 m^2	112±16	NA
Urine uromodulin, μg/ml	26.0 (17.4–34.9)	25.7 (14.5–39.9)
Urine creatinine, mg/dl	87.9 (62.4–125.5)	151.5 (106.6–205.4)
Urine albumin, mg/L	3.7 (2–6.8)	7 (4–13)
Urine osmolality, mOsm/kg H_2O	296 (173–568)	740 (579–870)
Urine volume, ml/24 h	1612 (1189–2200)	NA
Uromodulin excretion, 24 h UER, in mg/24 h	41 (29–57)	NA
Urinary osmolar excretion, mOsm/24 h	762 (620–940)	NA
Urinary creatinine excretion, mg/24 h	1399 (1134–1789)	NA
24-h urinary creatinine clearance, ml/min	124±33	NA
Ultrasonography data		
Kidney length, mm	110±8	NA
Kidney volume, cm^3	136±34	NA

Values are expressed as mean±SD, median (25th–75th percentile), or percentage, as appropriate. For urine data, values were measured in 24-hour urine in the Swiss Kidney Project on Genes in Hypertension (SKIPOGH) and in morning spot urine in the Cohorte Lausannoise (CoLaus) study. BMI, body mass index; $eGFR_{creatinine}$, eGFR calculated by 24-hour creatinine clearance; $eGFR_{cystatin\ C}$, eGFR calculated by cystatin C; UER, uromodulin excretion rate; NA, not available.

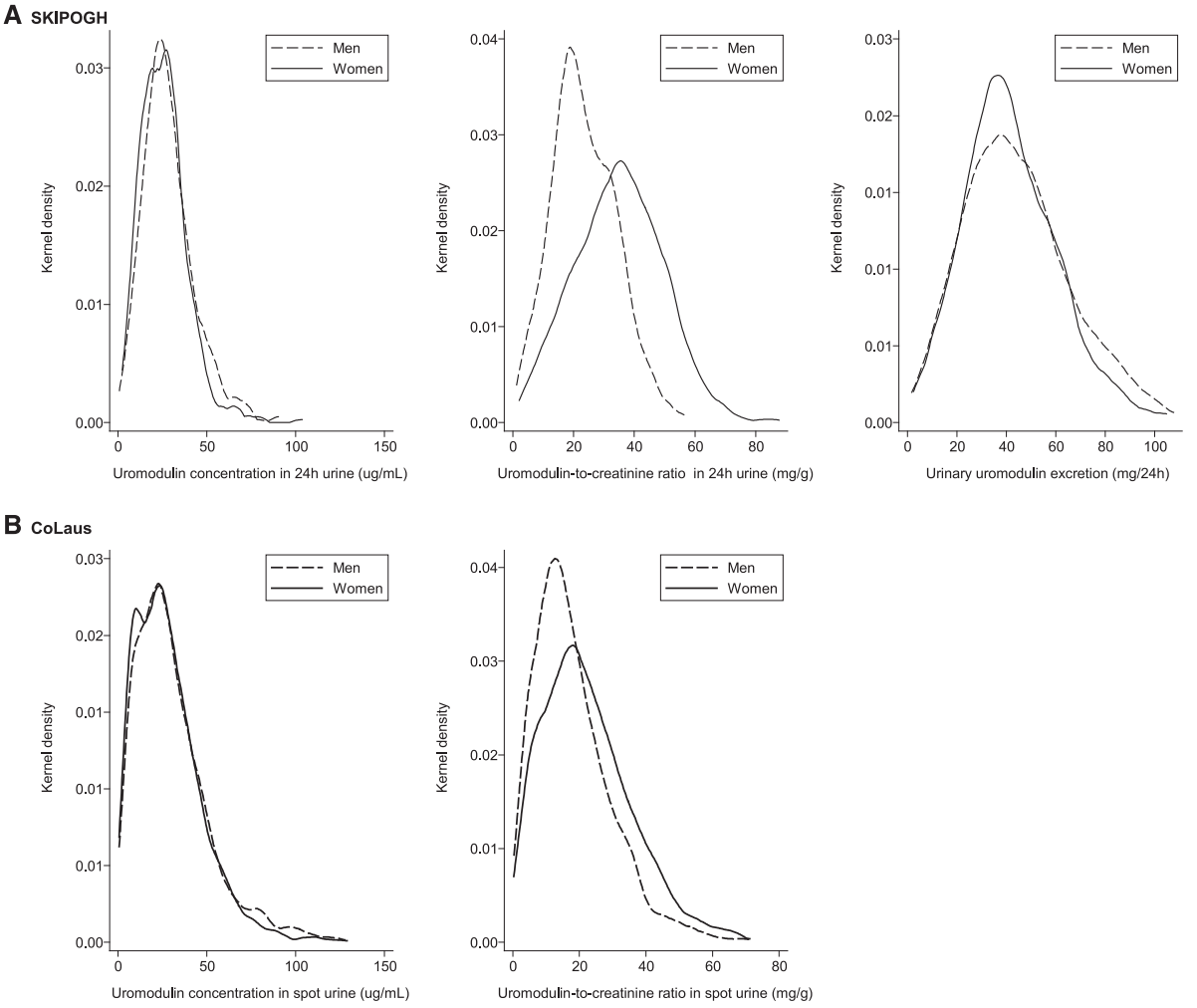

Figure 1. | Distribution of uromodulin according to sex. (A) Swiss Kidney Project on Genes in Hypertension (SKIPOGH). (B) Cohorte Lausannoise (CoLaus).

between 24-hour UER and 24-hours urine volume was not explained by differences in completeness of urine collection (see Supplemental Material).

Associations between Urinary Uromodulin and Markers of Glomerular Filtration

We found positive associations between 24-hour UER and eGFR (SKIPOGH) and between spot uromodulin concentrations and eGFR (CoLaus) (Table 3, model 1). For both cohorts, the association between urinary uromodulin and creatinine-based eGFR was not perfectly linear, with different results obtained for participants with eGFR<90 ml/min per 1.73 m^2 compared with eGFR ≥90 ml/min per 1.73 m^2 (Figure 2, A and B). Stratified results by eGFR are presented in Table 3. Further adjustment for creatinine excretion in CoLaus and SKIPOGH did not alter these results. Similar results were obtained with use of the Cockroft formula or CKD-EPI formula not standardized for body surface area (Supplemental Material). Furthermore, in SKIPOGH the cystatin-based eGFR also showed a significant association between uromodulin and eGFR<90 ml/min per 1.73 m^2, but not above. In SKIPOGH, a linear positive association between urinary creatinine clearance and 24-hour UER was found (Figure 3A). All the analyses were repeated after winsorizing of outliers (>99th or <1st percentile) of 24-hour UER and after exclusion of those with 24-hour urine volume <500 ml, with similar results.

Associations between Urinary Uromodulin and Microalbuminuria

No association was found between log-transformed albumin excretion and square-root–transformed uromodulin excretion adjusted for age, sex, body height and weight, eGFR, diabetes, hypertension, and creatininuria (regression coefficient β=−0.02 [95% confidence interval (95% CI), −0.05 to 0.02]; P=0.44). In CoLaus, we also found no association with square-root–transformed urinary albumin concentration (β=−0.03 [95% CI, −0.07 to 0.01]; P=0.09).

Associations between Urinary Uromodulin and Anatomic Markers of Renal Mass

In SKIPOGH participants, the 24-hour UER was positively and linearly associated with ultrasonography-assessed renal

Table 2. Clinical correlates of urinary uromodulin excretion (mg/24 hours) (dependent variable) in the Swiss Kidney Project on Genes in Hypertension (*n*=817)

Independent Variable	Unadjusted		Model 1		Model 2	
	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Age (per 10 yr)	−0.09 (−0.15 to −0.02)	0.006	−0.11 (−0.18 to −0.04)	0.002	−0.04 (−0.11 to 0.04)	0.34
Sex (female versus male)	−0.26 (−0.47 to −0.06)	0.01	−0.30 (−0.58 to 0.01)	0.06	0.096 (−0.22 to 0.42)	0.61
Body height (per 5 cm)	0.01 (0.04 to 0.16)	0.001	−0.02 (−0.11 to 0.08)	0.70	−0.05 (−0.14 to 0.05)	0.31
Body weight (per 5 kg)	0.04 (<0.01 to 0.08)	0.04	0.03 (−0.02 to 0.08)	0.25	0.03 (−0.08 to 0.02)	0.27
Smoking (yes versus no)	−0.04 (−0.29 to 0.21)	0.76	−0.04 (−0.27 to 0.19)	0.74	−0.03 (−0.26 to 0.19)	0.76
Diabetes (yes versus no)	−0.83 (−1.39 to −0.27)	0.004	−0.76 (−1.30 to −0.22)	0.01	−0.67 (−1.21 to −0.14)	0.01
Hypertension (yes versus no)	−0.20 (−0.47 to 0.07)	0.14	−0.07 (−0.37 to 0.23)	0.67	−0.05 (−0.35 to 0.24)	0.78
Diuretic use (yes versus no)	0.08 (−0.45 to 0.61)	0.77	0.34 (−0.20 to 0.87)	0.22	0.32 (−0.20 to 0.85)	0.24
Urinary volume (in ml)	1.22 (0.98 to 1.45)	<0.001	1.29 (1.06 to 1.52)	<0.001	1.16 (0.93 to 1.40)	<0.001
Urinary creatinine excretion (per mg/24 h)	1.64 (1.20 to 2.08)	<0.001	–		1.53 (0.96 to 2.10)	<0.001

Uromodulin excretion is square-root transformed. The coefficient stands for the regression coefficient β between urinary square-root uromodulin excretion (mg/24 h) and each independent variable. Urinary volume and creatinine excretion are log transformed. Model 1 adjusted for age, sex, body height and weight, smoking, hypertension, diabetes, urinary volume, and diuretic use. Model 2 adjusted as for model 1 plus 24-hour urinary creatinine excretion. 95% CI, 95% confidence interval.

length and volume in univariate and multivariate models (Figure 3, B and C, and Table 3).

Associations between 24-Hour UER, Urinary Electrolytes, and Osmolality

In SKIPOGH, we found positive associations between 24-hour UER and all electrolytes tested (Table 4). Associations between 24-hour UER, potassium, and magnesium excretion were no longer statistically significant when 24-hour urinary creatinine excretion was introduced in the model. The association between urinary osmolar excretion and 24-hour UER is shown in Figure 3D.

Positive associations were also detected between spot uromodulin concentration and urinary electrolytes in CoLaus (Table 4). Adjustment for urinary creatinine weakened most of the associations, yet uromodulin remained positively associated with potassium, chloride, and sodium. These results were unchanged when we excluded participants with a 24-hour urine volume <500 ml (*n*=7).

Discussion

The present study, based on two independent population-based cohorts, reveals that the daily rate of uromodulin excretion (24-hour UER) is positively associated with urine volume and the excretion rate of creatinine and is negatively associated with age and diabetes. Urinary uromodulin is positively associated with urinary electrolytes and osmolality as surrogate markers of tubular function. Furthermore, 24-hour UER is positively associated with ultrasonography-assessed renal length and volume. These data suggest that urinary uromodulin can be considered as a marker of tubular function and mass at a population level. In both cohorts, the association between urinary uromodulin and eGFR is positive and linear when eGFR is <90 ml/min per 1.73 m^2. Above that threshold, the relationship is flat, suggesting that the tubular production of uromodulin reaches a plateau.

To our knowledge, determinants of uromodulin other than glomerular filtration have not been studied before at a population level. Small studies have described negative associations between uromodulin, age (11), and diabetes (25). A rat study reported positive associations between uromodulin and urinary volume (26), but another did not (27). Others have reported that uromodulin is related to dietary salt intake (28). Importantly, these earlier studies used various assays and storage protocols, which hampered conclusions because analytical methods have a strong influence on uromodulin concentrations (22). In the present study, uromodulin was centrally measured through use of well established analytical procedures and ELISA (1,22). Although uromodulin concentrations were similar in 24-hour urine and spot urine, we used 24-hour urine to assess the determinants of uromodulin excretion because concentrations in spot urine samples are more likely to be influenced by hydration status.

We demonstrate that age, urinary creatinine excretion, diabetes, and urinary volume are independent factors associated with 24-hour uromodulin excretion, whereas others, such as sex and body height, are not. In this context, the role of urinary creatinine merits attention: Adjustment for urinary creatinine excretion altered the results. For

Table 3. Associations of 24-hour urinary uromodulin excretion with eGFR, 24-hour creatinine clearance, kidney length, and kidney volume and of spot uromodulin concentration with eGFR

Independent Variable	Unadjusted		Model 1		Model 2	
	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
SKIPOGH (based on uromodulin excretion in mg/24 h)						
$eGFR_{creatinine}$ (*n*=817)	0.01 (0.01 to 0.02)	<0.001	0.01 (0.002 to 0.02)	0.02	0.01 (0.01 to 0.23)	0.002
<90 ml/min per 1.73 m² (n=*241*)	0.04 (0.02 to 0.06)	<0.001	0.04 (0.02 to 0.06)	<0.001	0.04 (0.02 to 0.06)	<0.001
≥90 ml/min per 1.73 m² (n=*576*)	0.002 (−0.01 to 0.01)	0.70	0.003 (−0.01 to 0.02)	0.61	0.007 (−0.01 to 0.02)	0.32
$eGFR_{cystatin\ C}$ (*n*=723)	0.02 (0.01 to 0.03)	<0.001	0.018 (0.01 to 0.03)	0.001	–	
<90 ml/min per 1.73 m² (n=*60*)	0.06 (0.03 to 0.09)	<0.001	0.06 (0.03 to 0.09)	<0.001	–	
≥90 ml/min per 1.73 m² (n=*663*)	0.02 (0.01 to 0.03)	0.001	0.01 (−0.003 to 0.02)	0.12	–	
24-h creatinine clearance	0.01 (0.01 to 0.02)	<0.001	0.01 (0.01 to 0.02)	<0.001	–	
Kidney length	0.03 (0.02 to 0.05)	<0.001	0.02 (0.01 to 0.04)	0.002	0.02 (0.01 to 0.04)	0.01
Kidney volume	0.007 (0.004 to 0.01)	<0.001	0.008 (0.003 to 0.01)	0.001	0.007 (0.002 to 0.01)	0.002
CoLaus (uromodulin concentration in μg/ml)						
eGFR (*n*=5706)	0.01 (0.006 to 0.01)	<0.001	0.004 (0.001 to 0.09)	0.03	0.01 (0.01 to 0.02)	<0.001
<90 ml/min per 1.73 m² (*n*=3368)	0.02 (0.01 to 0.02)	<0.001	0.01 (0.01 to 0.02)	<0.001	0.02 (0.01 to 0.02)	<0.001
≥90 ml/min per 1.73 m² (*n*=2338)	−0.01 (0.02 to 0.0004)	0.06	−0.02 (−0.03 to −0.05)	0.01	−0.006 (−0.02 to 0.01)	0.41

The 24-hour urinary uromodulin excretion was the dependent variable in the Swiss Kidney Project on Genes in Hypertension (SKIPOGH). Uromodulin concentration was the dependent variable in the Cohorte Lausannoise (CoLaus) study. Urinary uromodulin is square-root transformed. Model 1: adjusted for age, sex body height, body weight, diabetes, arterial hypertension, smoking, and 24-hour urinary volume (in SKIPOGH only). Model 2: adjusted as for model 1 plus urinary creatinine concentration in CoLaus and +24-hour creatinine excretion (mg/24 hours) in SKIPOGH. $eGFR_{creatinine}$, eGFR calculated by 24-hour creatinine clearance; $eGFR_{cystatin\ C}$, eGFR calculated by cystatin C; 95% CI, 95% confidence interval.

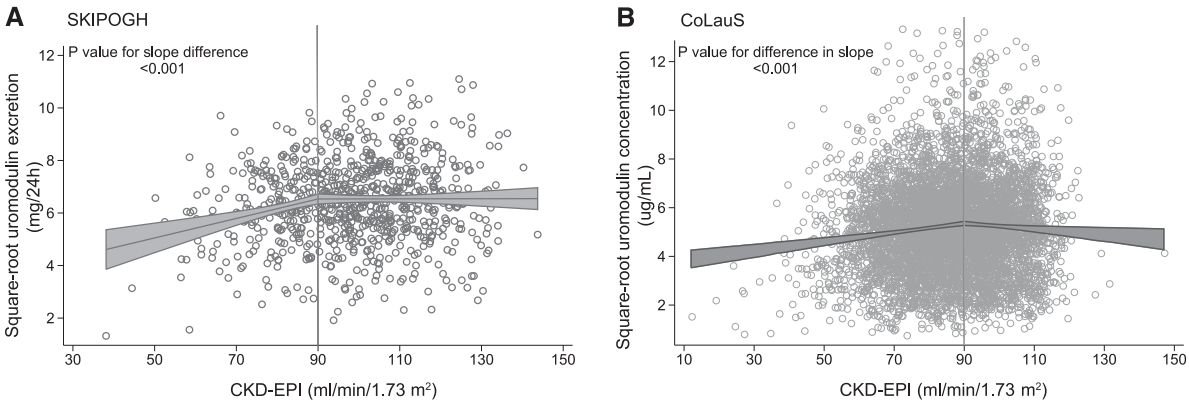

Figure 2. | **Scatterplots showing the association of the eGFR with urinary uromodulin.** (A) Swiss Kidney Project on Genes in Hypertension (SKIPOGH): positive association between eGFR and 24-hour urinary uromodulin excretion for eGFR below but not above 90 ml/min per 1.73m^2. (B) Cohorte Lausannoise (CoLaus): positive association between eGFR and uromodulin concentration for eGFR below but not above 90 ml/min per 1.73m^2. The eGFR was calculated with the CKD-Epidemiology Collaboration (CKD-EPI) equation. The vertical line represents the cut off eGFR 90 ml/min per 1.73m^2. When a spline term was used, a significant difference in slope between the two segments for both the SKIPOGH and CoLaus studies was found ($P<0.001$).

example, age was no longer a determinant of uromodulin when 24-hour creatinuria was introduced in the model. Because creatininuria depends on lean body mass and age, adjustment for creatinine might therefore lead to some form of overcorrection. The association between urinary volume and uromodulin excretion underlines the possible role of uromodulin in osmoregulation. Why diabetes was negatively associated with uromodulin remains unclear. This might be due to underlying tubular dysfunction independently of GFR, but considering the low number of patients with diabetes in this study, this finding needs confirmation in larger diabetes-specific studies.

We document positive associations between urinary uromodulin and 24-hour sodium, chloride, and potassium excretion, suggesting that uromodulin might influence the tubular handling of these electrolytes. In line with this finding, studies based on *in vitro* and *in vivo* mouse models have documented that uromodulin regulates transport processes operating in the TAL (*i.e.,* the functionally coupled sodium cotransporter NKCC2 and potassium channel ROMK) (4,29). A recent meta-analysis of the genetic determinants of urinary uromodulin revealed that variants in *KCNJ1* (ROMK), *CAB39*, and *SORL1* genes, which are all involved in regulating sodium transport in the TAL, were

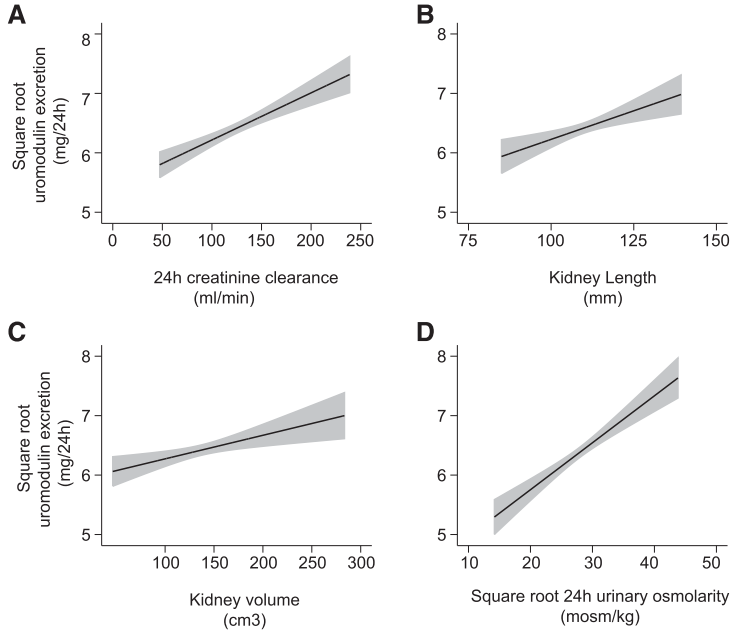

Figure 3. | **Age- and sex-adjusted associations of square rooted 24-hour uromodulin excretion with proxies of functional renal mass.** (A) 24-hour creatinine clearance; (B) kidney length; (C) kidney volume; and (D) urinary osmolar excretion.

Table 4. Association of urinary osmolality and electrolytes (dependent variables) with urinary uromodulin (independent variable)

Variable	Unadjusted		Model 1		Model 2	
	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Associations of 24-h urinary electrolyte and osmole excretions with uromodulin excretion (SKIPOGH)						
Urinary sodium excretion	2.07 (1.60 to 2.54)	<0.001	1.26 (0.81 to 1.72)	<0.001	0.98 (0.53 to 1.43)	<0.001
Urinary chloride excretion	2.16 (1.52 to 2.79)	<0.001	1.22 (0.61 to 1.83)	<0.001	0.90 (0.29 to 1.50)	0.004
Urinary potassium excretion	1.10 (0.74 to 1.47)	<0.001	0.43 (0.11 to 0.75)	0.010	0.07 (−0.23 to 0.37)	0.64
Urinary magnesium excretion	0.24 (0.17 to 0.32)	<0.001	0.12 (0.05 to 0.20)	0.001	0.06 (−0.01 to 0.13)	0.09
Urinary calcium excretion	0.38 (0.24 to 0.52)	<0.001	0.23 (0.09 to 0.4)	0.002	0.16 (0.02 to 0.30)	0.03
Urinary osmolar excretion	0.82 (0.63 to 1.01)	<0.001	0.54 (0.37 to 0.70)	<0.001	0.33 (0.18 to 0.48)	<0.001
Association of urinary electrolyte concentrations and osmolality with uromodulin concentration (CoLaus)						
Urinary sodium	1.87 (1.40 to 2.34)	<0.001	1.59 (1.14 to 2.04)	<0.001	1.63 (1.14 to 2.11)	<0.001
Urinary chloride	3.88 (3.34 to 4.42)	<0.001	3.45 (2.93 to 3.98)	<0.001	2.38 (1.82 to 2.94)	<0.001
Urinary potassium	6.40 (5.90 to 6.91)	<0.001	6.14 (5.64 to 6.65)	<0.001	2.63 (2.15 to 3.12)	<0.001
Urinary magnesium	0.81 (0.71 to 0.9)	<0.001	0.77 (0.67 to 0.86)	<0.001	0.02 (−0.07 to 0.10)	0.72
Urinary calcium	0.59 (0.45 to 0.73)	<0.001	0.54 (0.40 to 0.68)	<0.001	0.09 (−0.06 to 0.23)	0.25
Urinary osmolality	0.74 (0.69 to 0.79)	<0.001	0.68 (0.63 to 0.73)	<0.001	0.24 (0.20 to 0.29)	<0.001

All dependent variables as well as uromodulin are square-root transformed. For the Swiss Kidney Project on Genes in Hypertension (SKIPOGH), *n*=817; for the Cohorte Lausannoise (CoLaus) study, *n*=5706. Model 1: adjusted for age, sex, body height, body weight, eGFR, and 24-hour urinary volume (SKIPOGH only). Model 2: adjusted as for model 1 plus urinary creatinine concentration in CoLaus and 24-hour creatinine excretion (mg/24 h) in SKIPOGH. 95% CI, 95% confidence interval.

associated with uromodulin indexed to urinary creatinine. Although uromodulin remained associated with these urinary electrolytes after adjustment for confounders, these associations should not be overinterpreted, considering the influence of diet on sodium, chloride, and potassium excretion and handling at tubular level.

Positive associations were observed between 24 hours calcium excretion and uromodulin. Calcium excretion is less influenced by dietary factors and reflects therefore more closely the TAL function. This is exemplified in patients with Bartter syndrome due to NKCC2 dysfunction, who present with hypercalciuria irrespective of diet (30). The positive association between uromodulin and urinary osmolality is of interest because the latter parameter also reflects TAL activity. A potential role of uromodulin in osmoregulation has been suggested by mouse studies: For example, *Umod* knockout mice show NaCl wasting and impaired urinary concentration (3).

The associations between electrolytes, osmolality, and uromodulin, which contrast with the lack of association between uromodulin and microalbuminuria, suggest that the production and urinary excretion of uromodulin may reflect tubular function in the general population. This hypothesis will require more studies in order to disentangle potential confounding factors, such as diet and/or fluid intake.

To our knowledge, this study provides the first evidence that urinary uromodulin excretion correlates positively with ultrasonography-assessed renal length and volume parameters. Previous studies suggest that renal dimensions reflect nephron number and tubular function (31,32). The associations between uromodulin excretion and renal dimensions therefore further support the hypothesis that urinary uromodulin is a marker of tubular mass.

The relationship between urinary uromodulin excretion and glomerular filtration has long been debated, with some studies showing positive associations (11,12) and others not (33). Our data demonstrate a linear, positive association between uromodulin and eGFR, but only when eGFR is $<$90 ml/min per 1.73 m^2. These findings may explain the contradicting results of previous studies. They also indicate that uromodulin excretion is not a good surrogate marker of glomerular function, but instead offers information on renal (more precisely tubular) function. In fact, this observation is not surprising because uromodulin is exclusively produced by the TAL and directly released in the urine. The flat relationship between urinary uromodulin and eGFR$>$90 ml/min per 1.73 m^2 suggests that the production of uromodulin may reach a plateau and follow Michaelis-Menten kinetics, irrespective of further increase in GFR. Alternatively, the flat relationship could reflect the reduced accuracy of creatinine-based eGFR at higher GFR (19). In favor of this hypothesis, the relationship between uromodulin and urinary creatinine clearance remained positive and linear at higher eGFRs.

The major strengths of this study are the population-based design, the large sample size, the simultaneous measurements of renal anatomy parameters by ultrasonography and of tubular parameters, the replication cohort, the use of a standardized protocol across centers, and the central urine analysis. Limitations include the exclusion of nonwhites from these cohorts, and the complex interactions between the tubular handling of electrolytes, which cannot be fully elucidated in observational studies. Finally, the cross-sectional nature limits causal inferences.

In conclusion, the positive associations of urinary uromodulin with urinary electrolytes, osmolality, and kidney dimensions obtained by ultrasonography support the hypothesis that uromodulin excretion is a marker of tubular function in the general population.

Acknowledgments

The authors acknowledge Viviane Beaujean and Sebastien Druart (Université catholique de Louvain Medical School, Brussels, Belgium) for establishing the uromodulin ELISA. The authors wish to specially thank the recruitment teams, the administrative teams, and the study participants in the various cohorts.

The SKIPOGH study is supported by a grant from the Swiss National Science Foundation (FN 33CM30-124087), and the CoLaus study is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 3200B0-105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, and 33CS30-148401). Other funding sources for this study include the European Commission Seventh Framework Program (FP7/2007-2013 under grant 246539 of the Marie Curie Actions Programme and grant 305608 of the EURenOmics project), Fonds de la Recherche Scientifique and Fonds de la Recherche Scientifique Medicale, the Gebert Rüf Stiftung (project GRS-038/12), and the Swiss National Science Foundation (grants 310030-146490 and 32003B-149309 and the Swiss National Centre of Competence in Research Kidney Control of Homeostasis program).

Disclosures

None.

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Received: April 20, 2015 **Accepted:** September 15, 2015

M.P. and B.P. contributed equally to this work. M. Burnier, O.D., and M. Bochud codirected the study and contributed equally to this work.

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Tamm Horsfall Glycoprotein and Uromodulin: It Is All about the Tubules!," on pages 6–8.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.04230415/-/DCSupplemental.