Kidney360

# Healthy Women Have Higher Systemic Uromodulin Levels: Identification of Uromodulin as an Estrogen Responsive Gene

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## Key Points

- Serum uromodulin levels are higher in healthy female participants than healthy male participants.
- Serum uromodulin levels in participants with normal kidney function do not correlate with eGFR but do correlate with body mass index.
- Estrogen increases uromodulin production, likely because of noncanonical and half estrogen response elements in the *UMOD* gene.

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## Introduction

Uromodulin (gene: *UMOD*) is exclusively made by the kidney. It was originally identified in the 1950s as the most abundant protein in human urine but is now known to be released into the circulation as well. In the past decade, both the urinary and serum forms have gained attention as potential biomarkers for kidney function in the context of acute and chronic kidney diseases and as an overall marker of health.[1] However, there are few analyses focusing on a large number of healthy participants, and the ranges and physiological regulation of serum uromodulin have not been well established. Here, we measure serum uromodulin in a cohort of participants free from common comorbidities to contribute to the establishment of reference ranges for serum uromodulin and identify its determinants in healthy individuals.

## Methods

### Study Design

Serum samples were obtained from the Indiana Biobank which collects samples from those receiving care from a participating provider under an institutional review board-approved protocol with an informed consent allowing for broad use of specimens by approved researchers in accordance with the Declaration of Helsinki. Participating providers can be providing care at area hospitals or clinics. Specimens are linked to demographic and clinical data through the Indiana Network for Patient Care health information exchange. Exclusion criteria included diagnoses of acute or chronic kidney injury, diabetes, hypertension, or coronary artery disease. Samples taken during pregnancy or hospitalization were also excluded. Serum samples along with deidentified demographic information (sex, race, and age), prescription drug usage, and serum creatinine levels were provided by the Indiana Biobank for all currently available samples meeting the above criteria at the time the feasibility study was conducted in March 2021. Ethnicity data were missing for nearly half of participant samples, so this information was not reported or used in the analysis. Racial categories were established and reported by the Indiana Biobank.

### Serum Uromodulin Measurement

Serum uromodulin was measured in human samples using ELISA (Sigma Aldrich, RAB0751). The assay has an interassay coefficient of variation (CV) of <12% and an intraassay CV of <10% with a sensitivity of 40 pg/ml and a standard curve range of 40.96–10,000 pg/ml. Serum uromodulin was measured in mouse samples using ELISA (LifeSpan BioScience, LS-F21845). The assay has an interassay CV of <10% and an intraassay CV of <10% with a sensitivity of 1.875 ng/ml and a standard curve range of 3.125–200 ng/ml. All mice used were 8–12-week-old 129SvEv mice, which were bred and housed at the Association for Assessment and Accreditation of Laboratory Animal Care International accredited Indiana University Laboratory Animal Resource Center. All animal work was approved by the Institutional Animal Care and Use Committee and adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

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### Cell Studies

The mouse kidney thick ascending limb cell line[2] was cultured in ½ DMEM (Gibco, 10567014), ½ Ham's F-12 (Gibco, 31765035) media with 5% FBS (Gibco, A3840202), and ×1 penicillin–streptomycin (Gibco, 15140122). Cells were passaged and allowed to grow to 70%–80% confluency before culturing in serum-free medium for 24 hours. This was followed by overnight incubation in 17$\beta$-estradiol (Millipore Sigma, E2758) or ethanol vehicle in media containing charcoal-stripped FBS (Gibco, A3382101) before harvest.

### Western Blot

Samples were lysed in radioimmunoprecipitation assay Lysis and Extraction Buffer (ThermoFisher Scientific, 89901) with protease inhibitors (ThermoFisher Scientific, 78430). Equal amounts ($\mu$g) of protein lysates were separated on a 4–12% Bis-Tris gel (ThermoFisher Scientific, NW04127BOX) and transferred to a 0.45 $\mu$m polyvinylidene difluoride membrane (Millipore Sigma, IPVH00010). Blots were probed with rabbit anti-uromodulin (Abcam, ab207170) followed by donkey anti-rabbit horseradish peroxidase (Millipore Sigma, AP182P). All blots were developed using chemiluminescence reagents (ThermoFisher Scientific, 34095 and 34577). Blots were stripped (ThermoFisher Scientific, 21059) and probed with mouse anti–$\beta$-actin-horseradish peroxidase (Abcam, ab20272) as a loading control.

### Real-Time PCR Analysis

RNA was harvested from cell lysates using Trizol (ThermoFisher Scientific, 15596018) and used to generate cDNA using ReverTra Ace (Toyobo, TYB-QPX-201). For the real-time PCR reaction, the following primers were used: *UMOD* gene, gtgactctacgagtgaacagtg and aagcagccttggacactgag, and glyceraldehyde-3-phosphate dehydrogenase control, agcgagaccccactaacatc and ggcggagatgatgacccttt. Production of the target sequences was monitored using Thunderbird SYBR reagents (Toyobo, TYB-QPS-201) in an Applied Biosystems ViiA 7 system.

### Statistical Analysis

Serum uromodulin measurements along with demographic and clinical variables were used to create a database within SPSS Statistics (IBM). Independent variables of interest were extracted from deidentified patient charts by the Indiana BioBank from the Indiana Network for Patient Care health care exchange and included age, sex, body mass index (BMI), race, serum creatinine, and prescription drug usage. Race was self-reported to providers. Prescription drug usage was at any time in the patient chart. The serum creatinine and BMI values near the specimen collection were extracted from the patient chart. The eGFR was calculated from serum creatinine using the 2021 Chronic Kidney Disease Epidemiology Collaboration equation. Interaction terms between sex and age or sex and BMI were generated by mean-centering the continuous variables age and BMI and then creating an interaction term between the mean-centered variables and sex. The database was used to perform automated and directed multiple linear regression analyses with serum uromodulin as the dependent variable of interest. Automated linear modeling in SPSS was used to compare possible regression models for a given set of variables and identify candidate variables for directed analysis using a forward stepwise model selection. Variables were included based on the Akaike Information Criterion second-order estimate to measure how well each model fits the data. The subgroup-directed linear regressions were performed with the participants divided by sex. All other analyses were performed in GraphPad prism. The Mann–Whitney $U$ test was used to compare nonparametric datasets. Simple linear regression was used to determine whether there was a relationship between two continuous variables. For datasets with multiple treatment conditions, a one-way ANOVA was performed with embedded comparisons between two individual groups. Effect sizes for one-way ANOVA were calculated from the ANOVA outputs using the $\eta^2$ method. The threshold for significance was set to $\alpha$=0.05. Outliers (Tukey method) were removed for analyses but were included in the ranges to show the distribution of the data. To ensure that our results were not biased by the increased number of female participants included in this study, we generated 30 random subsamples of the female dataset cohort using the RANDARRAY function in Microsoft Excel that included an equivalent number of participants as the male dataset. Each subsample was compared with the male cohort using a two-sample $t$ test, and the results were consistent with the findings from the full dataset.

## Results

We measured circulating uromodulin levels for a cohort of healthy human participants (Table 1) available from the Indiana University Biobank. Healthy participants showed a wide range of circulating uromodulin levels (Table 1). Automated linear modeling in SPSS using relevant predictor variables extracted from deidentified patient charts identified sex and BMI as significant ($P < 0.05$) predictors of serum uromodulin levels (Supplemental Table 1). We used these variables to generate a model using multiple linear regression. The default participant for the model was a female with a BMI of 15 and had a constant value of 201.6±31.4 ng/ml uromodulin. Male sex decreased this by 50.7±22.1 ng/ml ($P = 0.02$). For each increase in BMI of a single unit, there was a corresponding drop in uromodulin of 2.2±1.1 ng/ml ($P = 0.04$, Supplemental Table 2). Sex and BMI remained significant predictors of serum uromodulin levels when the model was adjusted for race and age (Supplemental Table 2). Female participants showed significantly higher average levels (Figure 1, A and B, Table 1) than male participants. Because previous studies in cohorts that included participants with compromised kidney function have suggested that uromodulin levels are associated with eGFR,[3–7] we indexed serum uromodulin levels to eGFR and the difference between male participants and female participants was still significant (Figure 1C). In addition, eGFR was not identified as a significant predictor within the automatic linear model, did not show significance as a variable when added to the multiple linear regression, and its addition to the model did not change the significance of sex and BMI in predicting serum uromodulin levels (Supplemental Table 2).

Ranges for participants by age group and sex are presented in Table 2. While both male and female participants seem to have declining average values within the ranges as they

**Table 1. Demographic and measured variables in male and female participants**

| Variable | Overall ($N$=380) | Male ($n$=71) | Female ($n$=308) | $P$ Value |
|---|---|---|---|---|
| **Race** | | | | |
| Asian or Pacific Islander | 3 (0%) | 1 (1%) | 2 (0%) | 0.46 |
| Black or African American | 47 (12%) | 8 (11%) | 39 (13%) | 0.84 |
| Multiracial | 1 (0%) | 1 (1%) | 0 (0%) | 0.19 |
| Other/unknown | 88 (23%) | 9 (13%) | 79 (26%) | 0.019 |
| White | 241 (63%) | 52 (73%) | 188 (61%) | 0.057 |
| Age, yr | 32.6±13.8 | 33.9±17.5 | 33.1±12.9 | 0.35 |
| BMI[a] | 28.1±7.6 ($n$=161) | 28.5±7.1 ($n$=26) | 27.5±7.7 ($n$=135) | 0.76 |
| Serum creatinine (mg/dl)[b] | 0.84±0.16 ($n$=358) | 0.97±0.20 ($n$=63) | 0.82±0.13 ($n$=295) | <0.0001 |
| eGFR (CKD-EPI, ml/min) | 101.2±18.8 ($n$=358) | 104.8±22.5 ($n$=63) | 97.7±17.8 ($n$=295) | 0.1 |
| Serum uromodulin (ng/ml) | 135.0±94.7 | 101.9±54.4 | 145.7±100.2 | 0.001 |
| Serum uromodulin/eGFR (ng/ml per milliliter per minutes) | 1.38±1.00 ($n$=358) | 0.99±0.54 ($n$=63) | 1.55±1.06 ($n$=295) | 0.0006 |

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
[a]Range of (−6076 to 1112) days difference from serum specimen collection (−1183±1514 days).
[b]Range of (−9452 to 7045) days difference from serum specimen collection (−94±845 days).

age (Table 2), a simple linear regression between serum uromodulin and age in both male and female participants suggests that only female participants exhibit a trend ($P$ = 0.053) toward decreasing serum uromodulin with age (Figure 1, D and E). However, adding an interaction term between sex and age to the possible variables for automatic linear modeling did not change the results, and the interaction term was not identified as a significant predictor.

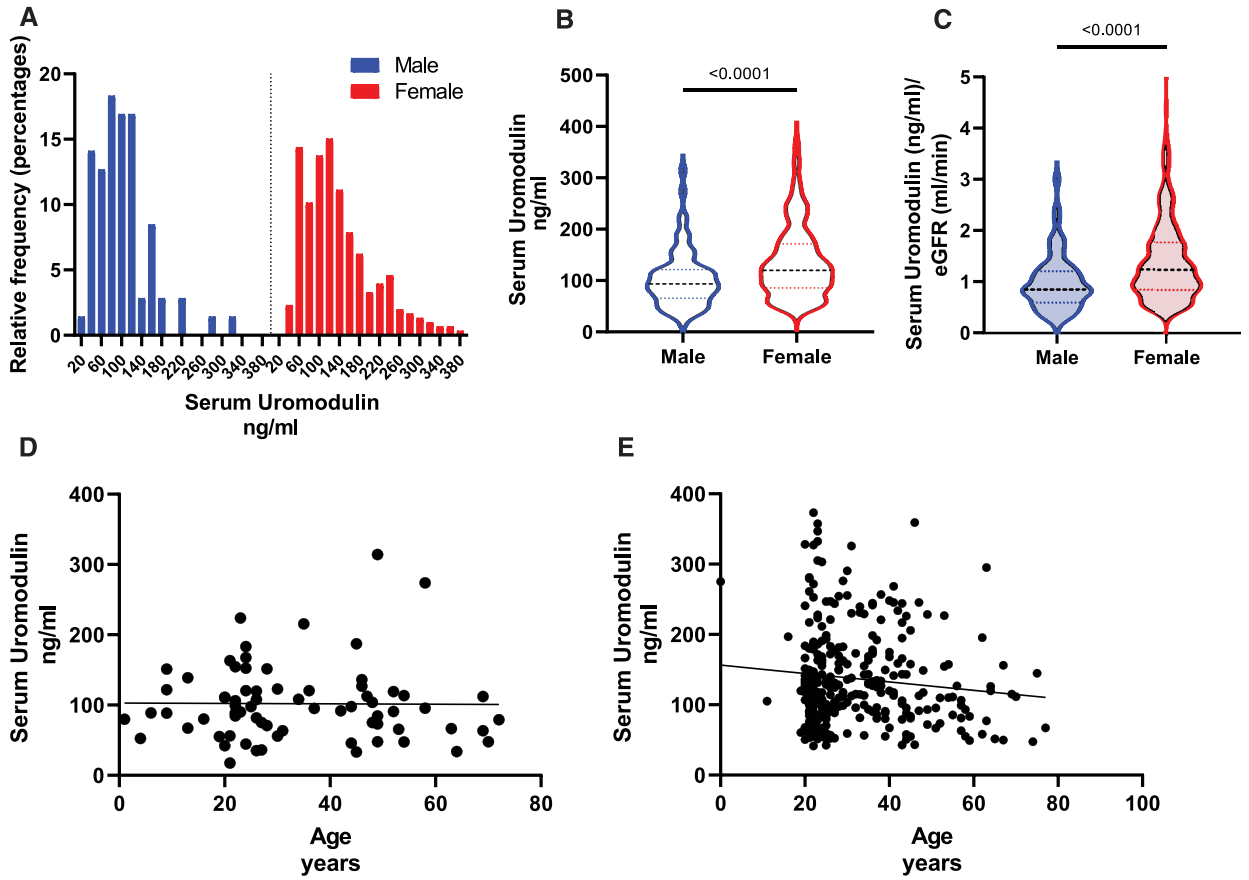


**Figure 1. Serum uromodulin is increased in healthy female participants.** (A) Distribution of serum uromodulin levels for female (red) and male (blue) participants. (B) Serum uromodulin levels are higher in female than male participants. (C) Serum uromodulin levels indexed to eGFR are higher in female than male participants. (D) Serum uromodulin is stable with age in male participants. $R^2$=8.44×10$^{-5}$, $P$ = 0.9394, F=0.005827. (E) There is a trend toward decreasing serum uromodulin with age in female participants. $R^2$=0.01228, $P$ = 0.0528, F=3.779.

**Table 2. Ranges of serum uromodulin (ng/ml) by age and sex**

| Age Range | Male | Female |
|---|---|---|
| **0–40 yr** | | |
| Sample size | 44 | 236 |
| Range | 17.5–223.7 | 41.4–1173 |
| Mean±SD | 102.2±46.9 | 144.9±96.5 |
| **41-60 yr** | | |
| Sample size | 21 | 58 |
| Range | 33.05–314.2 | 42.7–879.9 |
| Mean±SD | 111.2±70.6 | 141.6±120.0 |
| **61+ yr** | | |
| Sample size | 7 | 14 |
| Range | 33.9–192.8 | 47.5–295.1 |
| Mean±SD | 85.1±53.5 | 115.4±68.7 |

To identify a potential mechanism for increased serum uromodulin levels in female participants, we analyzed the *UMOD* locus in *Homo sapiens* and *Mus musculus* and found two noncanonical estrogen response elements (ERE)[8] and 29 canonical half-EREs[9] in the *Homo sapiens* and 45 canonical half-EREs in the *Mus musculus* sequence (Figure 2A). Consistent with this, serum uromodulin levels normalized to weight are higher in female mice (Figure 2B). In addition, treatment of mouse kidney thick ascending limb[2] cells with 10 pM–1 nM of 17$\beta$-estradiol increases uromodulin expression at the mRNA and protein level (Figure 2, C and D, Supplemental Table 3). These results suggest that female participants have higher serum uromodulin levels due to the estrogen responsiveness of the *UMOD* gene.

## Discussion

To the best of our knowledge, this study represents the largest survey of serum uromodulin levels in healthy participants without kidney disease or other associated comorbidities. The ranges identified were similar to what has been reported in other control patient cohorts.[7] We found that in participants without compromised kidney function, eGFR is not predictive of serum uromodulin levels, consistent with reports in healthy kidney donors.[10] This contrasts with studies of participants with compromised kidney function, which have shown that serum uromodulin is inversely correlated with eGFR.[7] When kidney function is declining, the effect of the residual kidney mass may be important in determining serum uromodulin levels, but other factors regulating uromodulin expression (*e.g.* response elements

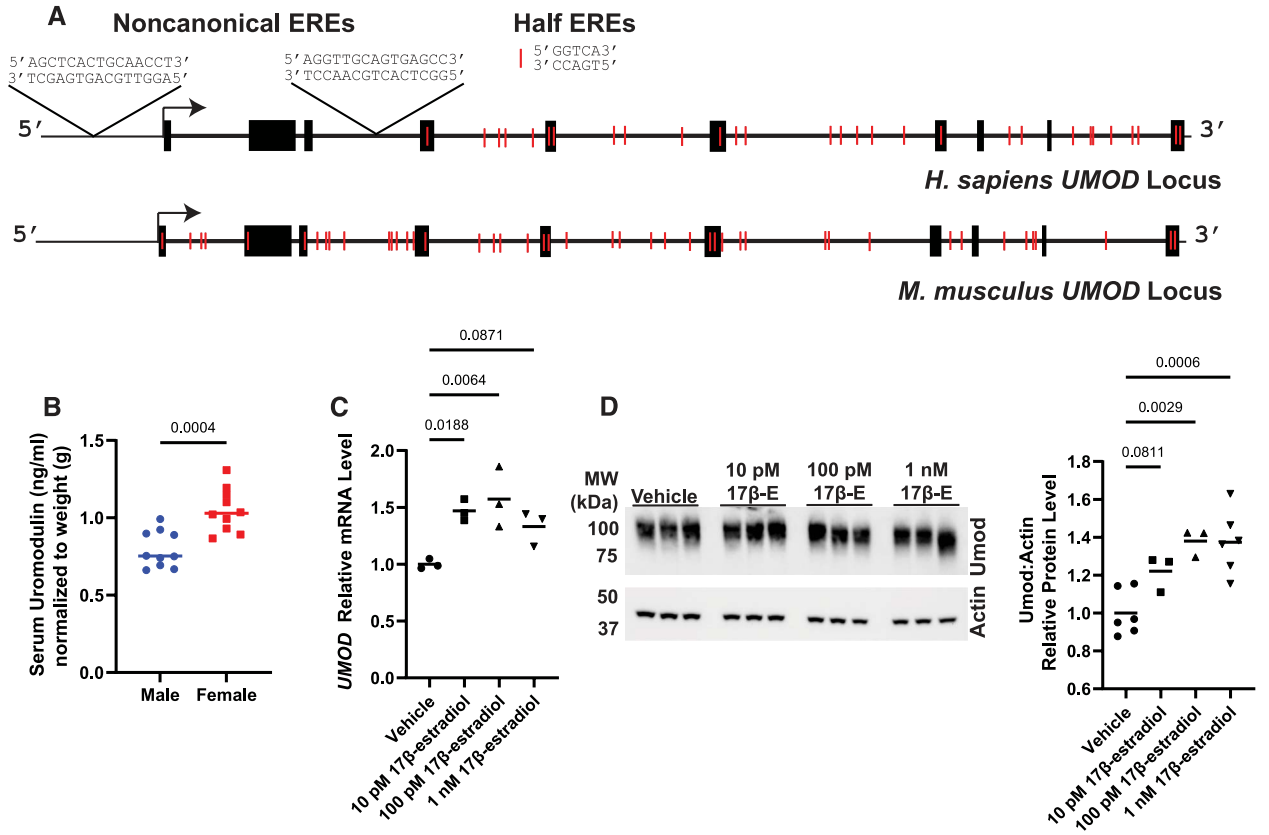


**Figure 2. The *UMOD* gene is responsive to estrogen.** (A) Genomic loci for *Homo sapiens* and *Mus musculus UMOD* genes. Translated exons are represented by black boxes, and the start site is indicated by the arrow. Sequences for the noncanonical complete EREs are shown in detail, and half EREs are indicated by red lines. (B) Female mice have higher serum uromodulin normalized to body weight. (C) Treatment of MKTAL cells with 17$\beta$-estradiol leads to increasing expression of the *UMOD* gene (one-way ANOVA, $P$=0.0120 with results of embedded multiple comparison $t$ tests shown). (D) Treatment of MKTAL cells with 17$\beta$-estradiol leads to increased levels of uromodulin relative to actin. Left panel, representative Western blot probed for uromodulin, top, and $\beta$-actin, bottom. Right panel, Western blot quantitation analysis (one-way ANOVA, $P$ = 0.0009 with results of embedded multiple comparison $t$ tests shown). ERE, estrogen response element; MKTAL, mouse kidney thick ascending limb.

in the *UMOD* gene) may supersede its importance in the setting of normal function. BMI was shown to be inversely correlated with serum uromodulin levels, consistent with studies that included those with and without kidney disease.[5] Female sex also emerged as an important driver of serum uromodulin levels, consistent with reports in participants with and without kidney disease that we have recently summarized.[11] Our analysis of the human and mouse *UMOD* genes described for the first time the potential for estrogen regulation, which was confirmed by *in vitro* 17$\beta$-estradiol treatment studies of a mouse thick ascending limb (TAL) cell line. These results are consistent with findings from a recent study by Scherberich *et al.* that found no difference in serum uromodulin levels between male and female participants younger than 18 years (median age 6 years) but significantly increased levels in female adults compared with male adults,[7] as children (including those who have begun puberty) are expected to have lower levels of estradiol than adults and these levels are similar between the sexes before the onset of puberty.

This study has important limitations. The relatively smaller number of male samples available from the Indiana University Biobank could have biased the data. However, a bootstrap analysis of 30 randomly generated subsamples of the female data showed consistent differences by sex. In addition, the population dataset is biased toward individuals who are willing to participate in discovery research (self-selection bias). Owing to the limitations of currently available banked samples, we were also not able to measure urinary uromodulin levels in the same participant cohort, repeated serum uromodulin levels in the same participants over time, or obtain genetic data for participants. The cell studies were limited by the lack of availability of a human-derived TAL cell line and were instead conducted in a mouse-derived TAL cell line.

The sexual dimorphism of serum uromodulin levels is particularly interesting in the context of the multiple functions ascribed to uromodulin. Uromodulin is a known immunomodulatory molecule, and women have a well-established decreased susceptibility to a variety of infectious diseases due to enhanced anti-infectious immunity.[12] This suggests that increased serum uromodulin levels could provide a beneficial immune boost to women, particularly those of child-bearing age, as we show here that serum uromodulin levels decline in women as they age. The relationship between BMI and serum uromodulin, although it has been reported previously, has not been explored mechanistically to our knowledge and it is unclear why increased BMI is correlated with decreased serum uromodulin. However, elevated BMI is also correlated with an increased risk of infection,[13] which is also consistent with uromodulin's immunomodulatory functions. Beyond uromodulin's immunomodulatory role, it is known to be protective in animal models of acute kidney injury.[14] A recent systematic review of the literature identified male sex as an independent risk factor for acute kidney injury,[15] which could be explained, in part, by their reduced serum uromodulin levels.

In conclusion, our results contribute to the development of reference ranges for serum uromodulin and provide the basis for future work exploring sexual dimorphism in its levels and their effect on human health. We identify the *UMOD* locus for the first time as an estrogen responsive gene, consistent with this study and reports from multiple groups describing higher serum uromodulin levels in female participants.

### Disclosures

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### Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A372.

Supplemental Table 1. Identification of significant predictors of serum uromodulin using automated linear modeling.

Supplemental Table 2. Linear models of serum uromodulin levels.

Supplemental Table 3. 17$\beta$-estradiol treatment of MKTAL cells.

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