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Hyperuricemia and Progression of CKD in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort Study

Kyle E. Rodenbach, BA,

University of Rochester Medical Center

Michael F. Schneider, MS,

Johns Hopkins Bloomberg School of Public Health

Susan L. Furth, MD, PhD,

Children's Hospital of Philadelphia

Marva M. Moxey-Mims, MD,

National Institute of Diabetes and Digestive and Kidney Diseases

Mark M. Mitsniefes, MD, MS,

Cincinnati Children's Hospital Medical Center

Donald J. Weaver, MD, PhD,

Levine Children's Hospital

Bradley A. Warady, MD, and

Children's Mercy Hospital

George J. Schwartz, MD

University of Rochester Medical Center

Abstract

Background—Hyperuricemia is associated with essential hypertension in children. No previous studies have evaluated the effect of hyperuricemia on progression of chronic kidney disease (CKD) in children.

Study Design—Prospective observational cohort study.

Corresponding Author: George J. Schwartz, MD, george_schwartz@urmc.rochester.edu.

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Setting & Participants—Children and adolescents (n=678 cross-sectional; n=627 longitudinal) with a median age of 12.3 (IQR, 8.6–15.6) years enrolled at 52 North American sites of the CKD in Children (CKiD) study.

Predictor—Serum uric acid (<5.5, 5.5–7.5, and >7.5 mg/dL).

Outcomes—Composite endpoint of either >30% decline in glomerular filtration rate (GFR) or initiation of renal replacement therapy.

Measurements—Age, sex, race, blood pressure status, GFR, CKD etiology, urine protein:creatinine ratio (<0.5, 0.5 to <2.0, 2.0 mg/mg), age- and sex-specific BMI >95th percentile, use of diuretics, and serum uric acid.

Results—162, 294, and 171 participants had initial uric acid < 5.5, 5.5–7.5, or > 7.5 mg/dL, respectively. Older age, male sex, lower GFR, and BMI > 95th percentile were associated with higher uric acid. We observed 225 instances of the composite endpoint over five years. In a multivariable parametric time-to-event analysis, compared to participants with initial uric acid <5.5 mg/dL, those with uric acid of 5.5–7.5 or >7.5 mg/dL had 17% shorter (relative time, 0.83; 95% CI, 0.62–1.11) or 38% shorter (relative time, 0.62; 95% CI, 0.45–0.85) times to event, respectively. Hypertension, lower GFR, glomerular CKD etiology, and elevated urine protein:creatinine ratio were also associated with faster times to the composite endpoint.

Limitations—The study lacked sufficient data to examine how use of specific medications might influence serum uric acid and CKD progression.

Conclusions—Hyperuricemia is a previously undescribed, independent risk factor for faster progression of CKD in children and adolescents. It is possible that treatment of children and adolescents with CKD with urate-lowering therapy could slow disease progression.

Index words

uric acid; urate; hyperuricemia; risk factor; chronic kidney disease (CKD); CKD progression; disease trajectory; pediatric kidney disease; children; adolescents; CKiD (Chronic Kidney Disease in Children); end-stage renal disease (ESRD); glomerular filtration rate (GFR); renal replacement therapy (RRT); renal function decline

Hyperuricemia is associated with development and progression of chronic kidney disease (CKD) in adults [1]. When kidney disease is present, decreased glomerular filtration may cause a rise in serum uric acid and provide additional risk for progressive decline in kidney function. Large, longitudinal studies confirm that hyperuricemia predicts the development of CKD in adults as well as the deterioration of kidney function in CKD patients [2–4].

The role of hyperuricemia in progression of CKD in children has not been extensively studied; however, a link between uric acid and essential hypertension may exist in children and adolescents. A number of studies have shown a positive relationship between uric acid and blood pressure (BP) in diverse populations of children [5–12]. Among these, one study suggested that uric acid level affects BP longitudinally [5]. Moreover, treating hyperuricemia with allopurinol in children with essential hypertension decreases BP and systemic vascular resistance [13–15]. In addition to the data for essential hypertension (where the prevalence of hyperuricemia is 89%), children with secondary hypertension also

appear to have increased rates of hyperuricemia (30%) [16]. To our knowledge, to date no studies have evaluated uric acid's effect on progression of CKD in children.

Animal studies have shown that uric acid can damage renal vessels in the absence of hypertension [17]. It is likely, therefore, that in the context of CKD, hyperuricemia can accelerate progression of kidney disease by causing vascular damage even if BP is adequately controlled.

While studies in adults confirm that hyperuricemia is, in fact, associated with more rapid reduction in kidney function, this has not yet been shown in children. If uric acid predicts faster deterioration of GFR in children with CKD, then addition of urate-lowering therapy to CKD treatment protocols for children may be warranted. The objectives of our current work are to determine the effect of uric acid on renal progression in children and adolescents with CKD in the presence of a variety of co-morbidities. We hypothesized that hyperuricemia is associated with increased kidney disease progression. If such an association exists, treatment of hyperuricemia in children and adolescents with CKD could potentially slow disease progression.

Methods

Participants

The CKD in Children (CKiD) study comprises a cohort of 891 children seen at a total of 55 pediatric nephrology centers across North America. The study design and conduct were approved by an observational study monitoring board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by the institutional review boards of each participating center. Briefly, participants had a median age of 11.1 (interquartile range [IQR], 7.7–14.8) years, 62% were male, and the median GFR was 47.8 (IQR, 34.1–62.9) mL/min/1.73 m². Participants were seen at annual follow-up study visits and provided data on renal, cardiovascular, neurocognitive, and growth parameters. Beginning in June 2008, serum uric acid was added to the laboratory panel as part of each annual visit.

Participants enrolled in the CKiD study had GFR measured by plasma disappearance of iothexol (mGFR) during the first two annual visits and during even numbered annual visits thereafter. Estimated GFR (eGFR) was determined during alternate annual visits using established estimating formulas, which were generated using CKiD data [18]. For the purposes of this analysis, GFR was defined as the mGFR when available and the eGFR during alternate years when GFR was not measured. A subgroup in whom mGFR was used exclusively was also examined.

At the time of analysis, 762 (86%) of the 891 CKiD participants had at least one study visit with uric acid data available; the visit with the first serum uric acid level was defined as the index visit. Of these 762 children, 678 also had data on age, sex, race, systolic and diastolic BPs, BP medication, mGFR or eGFR, BMI, diuretic usage, and urine protein-creatinine ratio (UPCR, in milligrams per milligram of creatinine) available at the index visit. These 678 children were included in the cross-sectional analysis and represented 52 of 55 CKiD sites.

From these 678 children, 627 had sufficient follow-up data available to determine time to >30% decline in GFR or time to renal replacement therapy (RRT) and served as the study population of our time-to-event analysis. Greater than 30% decline in GFR over 1–3 years of follow-up has previously been established as a strong and consistent surrogate for end stage renal disease in cohort studies [19]. As a sensitivity analysis, we compared our results to those obtained using a >40% decline in GFR and a >50% decline in GFR.

Statistical Analyses

Because the distribution of uric acid was reasonably normal (see Figure 1), we used univariable and multivariable linear regression to examine the cross sectional relationship between serum uric acid and the following variables at the index visit: age, sex, race, BP status (systolic or diastolic BP > age-, sex-, and height-specific 95th percentile with or without anti-hypertensive medication; systolic and diastolic BP age-, sex-, and height-specific 95th percentile and using anti-hypertensive medications; systolic and diastolic BP age-, sex-, and height-specific 95th percentile and not using anti-hypertensive medications), GFR, CKD etiology (glomerular vs. non-glomerular), UPCR (<0.5, 0.5 to <2.0, 2.0), age- and sex-specific BMI >95th percentile, and use of diuretics. Proteinuria cut-off values were chosen to correspond to levels of risk previously described for this population [20].

Next, we assessed the impact of uric acid measured at the index visit on the time to the composite endpoint of either >30% decline in GFR at each visit after the index visit (compared to GFR at the index visit) or initiation of RRT. Uric acid was categorized as <5.5, 5.5–7.5, and >7.5 mg/dL in time-to-event analyses, as 5.5 and 7.5 mg/dL represent the approximate IQR of the distribution.

Univariable and multivariable parametric failure time models assuming a generalized gamma distribution of event times were used to assess the relationship between index visit values of uric acid and covariates with the composite event [21]. Relative times were used to quantify the strength of the relationship between both uric acid and covariates and the composite event. Specifically, relative times represent the time it takes for p% of the “exposed group” to develop the composite event divided by the time it takes for p% of the “unexposed group” to develop the composite event. We utilized regression models under the assumption of proportional times (i.e., the relative times did not depend on “p”). The appropriateness of the generalized gamma distribution was assessed by comparing the estimated survival curves based on the generalized gamma parameter estimates with that of the non-parametric Kaplan-Meier survival curve. All analyses used a 0.05 level of significance. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Descriptive Statistics

Median index visit uric acid concentration was 6.5 (IQR, 5.4–7.6) mg/dL (Figure 1). Descriptive statistics for the 678 individuals included in the cross-sectional analysis appear in Table 1. Median GFR was 58.1 mL/min/1.73 m²; 32% of CKiD participants had a

glomerular CKD diagnosis; 27% had UPCR of 0.5 to <2.0 mg/mg; and 13% had UPCR 2.0 mg/mg. Overweight participants (age- and sex-specific BMI >95th percentile) comprised 18% of the study population. Forty-four were taking diuretics.

Cross-sectional Analyses

In univariable regression models, older age, male sex, systolic and diastolic BP 95th percentile on anti-hypertensive medications, lower GFR, UPCR 0.5 mg/mg, and age- and sex-specific BMI >95th percentile were significantly associated with concurrently higher index visit serum uric acid concentration.

In the multivariable model (Table 2), those with systolic and diastolic BP 95th percentile and on anti-hypertensive medication had uric acid values that were on average 0.26 (95% CI, -0.02 to 0.54) mg/dL higher than those with systolic and diastolic BP 95th percentile and not reporting use of anti-hypertensive medications. Those with systolic or diastolic BP >95th percentile had mean uric acid concentrations that were on average 0.29 (95% CI, -0.09 to 0.68) mg/dL higher than those with systolic and diastolic BP 95th percentile and with no anti-hypertensive medications. After adjustment, neither category of hypertension was associated with significantly higher mean index visit uric acid values. A similar scenario was observed for proteinuria, where UPCR 0.5 mg/mg was associated with higher index visit uric acid in the univariable analysis but not in the multivariable analysis. Moreover, even UPCR 2.0 mg/mg after adjustment was not associated with higher uric acid.

Each additional year of age was associated with a uric acid value that was 0.15 (95% CI, 0.12–0.17) mg/dL higher and each 10 ml/min/1.73m² decrement in index GFR was associated with a uric acid value that was 0.30 (95% CI, 0.25–0.35) mg/dL higher. Male sex and age- and sex-specific BMI >95th percentile were also associated with significantly higher uric acid. Race, CKD etiology, and use of diuretics were not associated with differences in uric acid concentration in univariable or multivariable analyses.

Time-to-Event Analyses

Descriptive statistics from the index visit for the 627 individuals included in the time-to-event analyses were stratified by index visit uric acid (<5.5 [n=162; 26%], 5.5–7.5 [n=294; 47%], and >7.5 mg/dL [n=171; 27%]) and appear in Table 3. The three groups had similar distributions of sex, race, CKD etiology, and diuretic use. Congruent with the cross-sectional results presented above, those with uric acid >7.5 mg/dL had the lowest GFRs and the greatest prevalence of UPCR 0.5 mg/mg.

We observed a total of 221 events (35% of 627): 172 with >30% decline in GFR and 49 with initiation of RRT prior to decline of >30% in GFR. Those with uric acid >7.5 mg/dL were more likely to attain the composite event (87 of 171 [51%]) than those with 5.5–7.5 (104 of 294 [35%]) or those with <5.5 mg/dL (30 of 162 [19%]).

Figure 2 shows the Kaplan-Meier survival curves (dashed lines) for the time from the index visit to the composite endpoint. The solid lines in the figure represent the survival curves estimated using a generalized gamma distribution and clearly indicate the appropriateness of

the parametric model fit to the data. It is evident from these curves that those with uric acid of 5.5–7.5 and >7.5 mg/dL at the index visit had shorter times to event compared to individuals with index uric acid <5.5 mg/dL (log-rank Test P-values =0.04 and <0.0001, respectively). For example, the 25th percentiles of the distribution of times to event were 3.57, 1.66, and 2.50 years for those with uric acid <5.5, 5.5–7.5, and >7.5 mg/dL, respectively. These estimated 25th percentiles directly yield the univariable relative times (shown in Table 4). Specifically, the ratio of the 25th percentile of those with index visit uric acid of 5.5–7.5 (2.50) to the 25th percentile of those with uric acid < 5.5 mg/dL (3.57) results in a relative time of 0.70 (95% CI, 0.51–0.96). This indicates that compared to those with an initial uric acid < 5.5 mg/dL, having a uric acid value of 5.5–7.5 was associated with 30% shorter time to event. Even more pronounced was the difference in time to event comparing those with an initial uric acid > 7.5 versus <5.5 mg/dL in which the relative time was 0.46 (i.e., 1.66/3.57; 95% CI, 0.33–0.65), indicating 54% shorter times to event in participants with an index uric acid > 7.5 mg/dL.

Additionally, age, systolic or diastolic BP >95%, systolic and diastolic BP 95% with medication, lower GFR, glomerular CKD etiology, and UPCR 0.5 were associated with significantly shorter times to >30% decline in GFR or initiation of RRT.

In the multivariable analysis, index uric acid >7.5 mg/dL remained a significant risk factor for faster arrival of the composite endpoint (relative time, 0.62; 95% CI, 0.45–0.85) with loss of significance in those with index uric acid 5.5–7.5 mg/dL (relative time, 0.83; 95% CI, 0.62–1.11). Systolic or diastolic BP >95th percentile remained significant (relative time, 0.60; 95% CI, 0.44–0.83), while systolic and diastolic BP 95th percentile with medication did not (relative time, 0.80; 95% CI, 0.62–1.03). The effect of frank hypertension appeared to be quantitatively similar to the effect of hyperuricemia in reducing the time to the composite event. Those with lower initial GFR, glomerular CKD etiology, and UPCR 0.5 also reached the composite endpoint significantly faster than those in the corresponding reference group. Age, male sex, race, age- and sex specific BMI >95% and use of diuretics were not associated with time to event.

If only mGFR was used to determine the outcome of interest (and not both mGFR and eGFR), the multivariable relative times comparing the groups with the two highest uric acid values to those with the lowest uric acid were 0.91 (95% CI, 0.66–1.25) and 0.68 (95% CI, 0.48–0.95), respectively. The similarity between these relative times and those that we report in Table 4 indicates our results are not sensitive to using the composite mGFR/eGFR to define the outcome.

We conducted two additional analyses using composite endpoints of >40% decline in initial GFR or initiation of RRT as well as >50% decline in initial GFR or initiation of RRT to assess how sensitive our inferences were to the definition chosen, i.e., >30% decline or RRT. Our primary findings were preserved using the 40% cutoff, where the multivariable relative time for uric acid, comparing those with >7.5 to those with <5.5 mg/dL was 0.66 (95% CI, 0.45–0.98) and similar to the 0.62 (95% CI, 0.45–0.85) reported in Table 4 when >30% was used. For uric acid of 5.5–7.5 vs. <5.5 mg/dL, the multivariable relative time was 0.96 (95% CI, 0.66–1.38) compared to 0.83 (95% CI, 0.62–1.11) reported in Table 4 when

>30% was used. When using the 50% cutoff, uric acid was not associated with faster decline in GFR for either of these groups; however, only 54 participants were observed to have >50% decline, substantially less than the 96 observed to have at least a 40% decline or the 172 observed to have at least a 30% decline.

Discussion

Age, male sex, initial GFR, and age- and sex-specific BMI >95% were positively associated with elevated serum uric acid in the multivariable cross-sectional analysis. Race, systolic or diastolic BP >95% or systolic or diastolic BP 95% with antihypertensive medications, CKD etiology (glomerular vs. non-glomerular), and use of diuretics were not associated with significantly higher uric acid. Considering the positive data for this association in adults and children with primary hypertension, finding that neither category of hypertension was associated with significantly higher uric acid on a cross-sectional basis was not expected. In studies of adults, elevated uric acid is associated with a 1.0- to 3.0-fold increased risk for hypertension over a range of follow-up intervals [1]. It is likely that in the setting of CKD in children and adolescents, variables other than blood pressure share a stronger relationship with uric acid on a cross-sectional basis, such as GFR.

Serum uric acid is associated with dietary fructose intake [22]. Findings in this study support this relationship, as individuals with age- and sex-specific BMI >95% had significantly higher serum uric acid than normal weight individuals (regression coefficient, 0.58; 95% CI, 0.28–0.87) in the cross-sectional, multivariable analysis. Interestingly, age- and sex-specific BMI >95% was not associated with faster arrival of the composite endpoint in the longitudinal analysis. This supports previous work suggesting that in the setting of CKD, other factors, including BP and CKD etiology drive disease progression [20]. On a longitudinal basis, these data indicate that serum uric acid > 7.5 mg/dL is an independent risk factor for faster progression to >30% decline in kidney function or initiation of RRT in children and adolescents with mild to moderate CKD at initial presentation. An upper limit of 7.5 mg/dL was chosen from the median index visit serum uric acid observed. A uric acid of 7.5 mg/dL represented the 73rd percentile, with only 27% of the population having uric acid >7.5 mg/dL at index. While having uric acid of 5.5–7.5 mg/dL was associated with faster decline in kidney function on a univariable basis, only those with uric acid >7.5 mg/dL had faster decline in the multivariable model. This indicates that 27% of the population had a modifiable risk factor (hyperuricemia) at the index visit that was found to be independently associated with faster decline in kidney function over five years of follow-up. The magnitude of association between uric acid and progression of CKD that we observed in the CKiD cohort was similar to what has been shown in adult populations. Specifically, we found a 1.61 (1/0.62) greater risk of CKD progression in those with the highest uric acid levels; this is comparable to the 1.0- to 3.0-fold increased risk of progressive decline in kidney function found in adults [1]. The largest among the adult studies (N=177,570) showed a 2.14-fold increased risk of ESRD for those in the highest compared to the lowest quartile of uric acid [23].

These findings are particularly noteworthy due to the absence of recommended target uric acid values in CKD patients. Treatment of so-called asymptomatic hyperuricemia is not

routine and, in fact, only within the last ten years have data suggested that elevated uric acid has the capacity to cause disease in the absence of overt clinical symptoms. At least ten studies have published data on normal values of uric acid in healthy children and adolescents; yet, even for healthy individuals, uniform reference standards are difficult to define. In general, serum uric acid increases from birth to adulthood, with no sex difference in serum values prior to puberty. Healthy post-pubertal males, however, have higher uric acid levels than age-matched females, which is believed to be due to elevations in estrogen in females at puberty [26–34]. In our large study of children with CKD, male sex was associated with significantly higher uric acid values than female sex (regression coefficient, 0.47; 95% CI, 0.24–0.70) in the multivariable model. However, the percentage of males with index visit uric acid >7.5 mg/dL was not greater than those with uric acid < 5.5 or 5.5–7.5 mg/dL (Table 3). Moreover, male sex was not associated with faster arrival at the composite endpoint. Together, these findings suggest that males may tolerate higher levels of uric acid than females. This would agree with studies in healthy populations, which suggest that uric acid values of 7.0–8.0 mg/dL are the upper limit of normal for healthy post-pubertal males [24–31].

While most studies in adults have found positive associations between uric acid and incident hypertension and CKD and several have shown a role for uric acid in CKD progression, not all findings have been positive. A large study of 3,693 patients in the Hypertension Detection and Follow-Up Program found that treatment of diuretic-induced hyperuricemia had no effect on changes in serum creatinine at one year [33]. Additionally, an analysis using the MDRD (Modification of Diet in Renal Disease) Study population found that while uric acid was associated with all-cause mortality, uric acid had no effect on kidney failure rates at ten years in multivariable models [34]. A recent small (N=54) study of patients with CKD found that normalization of uric acid with allopurinol decreased the rate of decline in kidney function and initiation of dialysis but had no effect on BP [35]. Additionally, in patients with CKD stage 5, both high and low levels of uric acid are associated with all-cause mortality at twenty-seven months, with the lowest risk for the middle three uric acid quintiles in a multivariable model [36].

Strengths of this study include the large sample size and five-year longitudinal follow-up of children and adolescents with a wide range of baseline kidney function and a broad spectrum of glomerular and non-glomerular disease etiologies. Furthermore, the longitudinal association with uric acid is independent of other factors associated with the decrement in GFR, including proteinuria and hypertension. This study also has several limitations. There was not sufficient data to describe relationships between specific medications and uric acid, although, as a group, diuretics did not appear to have an effect on uric acid or on time to the composite endpoint. It is also not possible to conclude from this analysis that uric acid has a causal role in CKD progression; although there is a significant association.

Serum uric acid is easily modified by several classes of pharmaceutical agents. Therefore, given the independent association between uric acid >7.5 and faster deterioration in kidney function, serum uric acid may represent a modifiable risk factor in CKD. Adult CKD patients treated with as little as 100 mg/d of allopurinol have significantly slower deterioration of kidney function compared to those on standard therapy [37–38].

Additionally, 100 mg/d of allopurinol has been shown to reduce proteinuria at four months in adults with diabetic nephropathy [39]. At 300 mg/d, allopurinol has been shown to reduce systolic and diastolic BPs, decrease C-reactive protein levels, and increase eGFR in adult hypertensive patients [40]. Accordingly, our findings in children and adolescents suggest that clinical trials investigating the use of allopurinol and other uricosuric agents in children and adolescents with CKD should be considered to determine if addition of urate-lowering therapy is warranted. Studies are also needed to evaluate whether changes in clinical practice, such as minimizing use of diuretics and/or preferential use of losartan, which has known uricosuric activity [41], will slow progression in children and adolescents with CKD.

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Figure 1.
Histogram depicting the distribution of serum Uric Acid at the index visit; median=6.5
(interquartile range, 5.4–7.6) mg/dL (N=678)

Figure 2.

Kaplan-Meier and conventional generalized gamma survival curves for the composite end-point of >30% decline in GFR or initiation of RRT.

Table 1

Descriptive Statistics at Index Visit

Characteristic	Value
No. of participants	678
Age, ye	12.3 [8.6–15.6]
Male Sex	60% (408)
White Race	66% (446)
Systolic or Diastolic BP > 95 th percentile ^a	14% (97)
Systolic and diastolic BP 95 th percentile	
receiving anti-HTN medication	57% (386)
Not receiving anti-HTN medication	29% (195)
mGFR or eGFR, ml/min/1.73m ²	58.1 [42.0–74.7]
Glomerular CKD etiology	32% (215)
UPCR	
<0.5 mg/mg	60% (410)
0.5 to <2.0 mg/mg	27% (181)
2.0 mg/mg	13% (87)
BMI [*] > 95 th percentile	18% (121)
Diuretic Use	6% (44)

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage); for continuous variables, as median [interquartile range].

BMI, body mass index; CKD, chronic kidney disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; HTN, hypertension; mGFR, measured glomerular

^aBP percentiles were determined using age-, sex-, and height-adjusted normal values.

* Age- and sex-specific BMI.

Table 2

Relationship between Indicated Characteristics at index visit and Index Visit Value of Uric Acid

Characteristics	Regression Coefficient (95% CI)	
	Univariable	Multivariable *
Age, per 1-y older	0.16 (0.13, 0.19)	0.15 (0.12, 0.17)
Male Sex (vs. female)	0.30 (0.02, 0.58)	0.47 (0.24, 0.70)
White Race (vs. non-White)	0.03 (−0.26, 0.32)	−0.07 (−0.31, 0.17)
Systolic or Diastolic BP >95 th percentile **	0.39 (−0.05, 0.83)	0.29 (−0.09, 0.68)
Systolic and diastolic BP 95 th percentile **		
receiving anti-HTN medication	0.66 (0.35, 0.97)	0.26 (−0.02, 0.54)
Not receiving anti-HTN medication	0 (reference)	0 (reference)
GFR, per 10 ml/min/1.73 m ² lower	0.30 (0.25, 0.35)	0.30 (0.25, 0.35)
Glomerular CKD etiology (vs. non-Glomerular)	−0.06 (−0.35, 0.24)	−0.02 (−0.31, 0.27)
UPCR		
<0.5 mg/mg	0 (reference)	0 (reference)
0.5–<2.0 mg/mg	1.05 (0.74, 1.36)	0.19 (−0.09, 0.47)
2.0 mg/mg	0.63 (0.22, 1.04)	−0.34 (−0.72, 0.05)
BMI *** > 95 th percentile (vs. 95 th)	0.69 (0.33, 1.05)	0.58 (0.28, 0.87)
Diuretic Use (vs. no diuretic use)	0.40 (−0.16, 0.96)	0.19 (−0.27, 0.66)

N=678. Regression coefficients that attained significance at $\alpha = 0.05$ level appear in bold.

CI, confidence interval; CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HTN, hypertension; UPCR, urine protein-creatinine ratio

* The multivariable model adjusted for all variables included in the table.

** BP percentiles were determined using age-, sex-, and height-adjusted normal values.

*** Age- and sex-specific BMI.

Table 3

Characteristics at the Index Visit by Category of Uric Acid

Characteristic	<5.5 mg/dL (n=162)	5.5–7.5 mg/dL (n=294)	>7.5 (n=171)	p-value ^a
Age, y	9.8 [6.7–13.2]	11.7 [8.1–15.0]	14.8 [12.2–16.8]	<0.001
Sex				0.5
Male	62%	58%	65%	
Female	38%	42%	35%	
Race				0.6
White	64%	68%	67%	
Non-White	36%	32%	33%	
BP Status ^b				0.002
BP > 95 th percentile	14%	15%	14%	
BP ≤ 95 th percentile				
receiving anti-HTN medication	44%	58%	65%	
Not receiving anti-HTN medication	43%	28%	21%	
GFR, ml/min/1.73m ²	71.9 [56.4–89.4]	55.9 [42.1–72.6]	45.5 [30.8–56.8]	<0.001
CKD etiology				0.4
Glomerular	33%	26%	29%	
Non-Glomerular	67%	74%	71%	
UPCR				<0.001
<0.5 mg/mg	73%	64%	43%	
0.5 to <2.0 mg/mg	16%	24%	41%	
2.0 mg/mg	11%	12%	16%	
BMI [*] percentile				<0.004
>95 th	16%	11%	27%	
≤95 th	84%	89%	73%	
Diuretic Use				0.3
Yes	6%	6%	9%	
No	94%	94%	91%	

Note: N=627. Values for categorical variables are given as number (percentage); for continuous variables, as median [interquartile range].

BMI, body mass index; CKD, chronic kidney disease; BP, blood pressure; GFR, glomerular filtration rate; HTN, hypertension; UPCR, urine protein-creatinine ratio

^aFor continuous characteristics, a Wilcoxon rank sum test was used; for categorical characteristics, a Cochran-Mantel-Haenszel test was used.

^bBP percentiles were determined using age-sex-height adjusted normal values.

* Age- and sex-specific BMI.

Table 4

Relationship between Indicated Characteristics at Index Visit and Subsequent Decline of >30% in GFR or Initiation of RRT

Characteristic	Relative Time (95% CI) ^a	
	Univariable	Multivariable ^b
Uric acid		
< 5.5 mg/dL	1.00 (reference)	1.00 (reference)
5.5–7.5 mg/dL	0.70 (0.51, 0.96)	0.83 (0.62, 1.11)
> 7.5 mg/dL	0.46 (0.33, 0.65)	0.62 (0.45, 0.85)
Age, per 1 year older	0.95 (0.93, 0.98)	0.99 (0.97, 1.02)
Male Sex (vs. Female)	0.97 (0.82, 1.16)	0.87 (0.71, 1.06)
White Race (vs. nonwhite)	1.19 (1.01, 1.42)	1.18 (0.97, 1.44)
Systolic or Diastolic BP > 95 th percentile ^c	0.44 (0.31, 0.61)	0.60 (0.44, 0.83)
Systolic and diastolic BP 95 th percentile ^c		
Receiving anti-HTN medication	0.60 (0.47, 0.78)	0.80 (0.62, 1.03)
Not receiving anti-HTN medication	1.00 (reference)	1.00 (reference)
GFR, per 10 ml/min/1.73m ² lower	0.86 (0.81, 0.91)	0.92 (0.87, 0.97)
Glomerular CKD etiology (vs. Non-Glomerular)	0.70 (0.56, 0.89)	0.75 (0.59, 0.95)
UPCR		
<0.5 mg/dl	1.00 (reference)	1.00 (reference)
0.5–2.0 mg/dL	0.49 (0.39, 0.62)	0.65 (0.51, 0.82)
2.0 mg/dL	0.24 (0.18, 0.33)	0.33 (0.25, 0.44)
BMI [*] >95 th percentile (vs. 95 th)	0.97 (0.77, 1.23)	1.17 (0.90, 1.53)
Diuretic Use (vs. no diuretic use)	0.85 (0.62, 1.16)	1.01 (0.69, 1.45)

Note: N=627 (221 events).

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; BP, blood pressure; GFR, glomerular filtration rate; HTN, hypertension; UPCR, urine protein-creatinine ratio

^aRelative times that attained significance at $\alpha = 0.05$ level appear in bold.

^bThe multivariable model included all variables that appear in the table.

^cBP percentiles were determined using age-, sex-, and height-adjusted normal values.

* Age- and sex-specific BMI.