Uric Acid and the Risks of Kidney Failure and Death in Individuals With CKD

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Background: Serum uric acid concentrations increase in chronic kidney disease (CKD) and may lead to tubular injury, endothelial dysfunction, oxidative stress, and intrarenal inflammation. Whether uric acid concentrations are associated with kidney failure and death in CKD is unknown.

Study Design: Prospective observational cohort study.

Settings & Participants: 3,885 individuals with CKD stages 2 to 4 enrolled in the Chronic Renal Insufficiency Cohort (CRIC) between June 2003 and September 2008 and followed up through March 2013.

Predictor: Baseline uric acid concentrations.

Outcomes: Kidney failure (initiation of dialysis therapy or transplantation) and all-cause mortality.

Results: During a median follow-up of 7.9 years, 885 participants progressed to kidney failure and 789 participants died. After adjustment for demographic, cardiovascular, and kidney-specific covariates, higher uric acid concentrations were independently associated with risk for kidney failure in participants with estimated glomerular filtration rates (eGFRs) ≥ 45 mL/min/1.73 m^2 (adjusted HR per 1−standard deviation greater baseline uric acid, 1.40; 95% CI, 1.12-1.75), but not in those with eGFRs < 30 mL/min/1.73 m^2. There was a nominally higher HR in participants with eGFRs of 30 to 44 mL/min/1.73 m^2 (adjusted HR, 1.13; 95% CI, 0.99-1.29), but this did not reach statistical significance. The relationship between uric acid concentration and all-cause mortality was J-shaped ($P = 0.007$).

Limitations: Potential residual confounding through unavailable confounders; lack of follow-up measurements to adjust for changes in uric acid concentrations over time.

Conclusions: Uric acid concentration is an independent risk factor for kidney failure in earlier stages of CKD and has a J-shaped relationship with all-cause mortality in CKD. Adequately powered randomized placebo-controlled trials in CKD are needed to test whether urate lowering may prove to be an effective approach to prevent complications and progression of CKD.

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Uric acid, the end product of purine metabolism in humans, is excreted largely by the kidneys. In chronic kidney disease (CKD), plasma uric acid concentrations increase due to reductions in glomerular filtration rate (GFR). Hyperuricemia is a hallmark of gout and is also a suspected risk factor for conditions accompanying metabolic syndrome, such as hypertension,[1,2] diabetes mellitus,[3] and cardiovascular diseases.[4-6] Uric acid can cause acute kidney injury, most notably in tumor lysis syndrome through precipitation and obstruction in tubules.[7] Uric acid may also lead to CKD and its progression by causing endothelial dysfunction,[8-11] activation of the renin-angiotensin-aldosterone system,[8,12] inflammation,[13,14] and oxidative stress.[15,16]

Several studies have suggested that higher uric acid concentrations are associated with the development of CKD.[17-19] Less is known about the association of uric acid concentrations with outcomes in CKD[20-22] and whether uric acid is simply a marker of lower estimated GFR (eGFR) or casually associated with adverse outcomes in CKD.[23] The distinction is important because uric acid concentration lowering has been proposed as a therapeutic strategy in CKD to prevent CKD progression and cardiovascular events.[24-27] We therefore studied whether uric acid concentrations are associated with adverse events in the Chronic Renal Insufficiency Cohort (CRIC), a prospective cohort study of individuals with established CKD.

Methods

Study Population

The CRIC Study is a multicenter prospective observational cohort study of individuals with mild to severe CKD that was designed to investigate risk factors for progression of CKD, cardiovascular disease, and mortality.[28] The CRIC Study enrolled 3,939 men and women aged 21 to 74 years between June 2003 and September 2008 across 7 clinical centers in the United States. Individuals were included if they met specific age-defined criteria for eGFR of 20 to 70 mL/min/1.73 m^2. Exclusion criteria included inability to provide consent, institutionalization, enrollment in competing studies, pregnancy, New York Heart Association class III or IV congestive heart failure, human immunodeficiency virus infection, multiple myeloma, polycystic kidney disease, renal cancer, cirrhosis, recent chemotherapy or immunosuppressive therapy, organ transplantation, or prior dialysis treatment for at least 1 month.[28-30]

The study protocol was approved by the institutional review boards of the participating centers and is in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants enrolled in CRIC. For purposes of this study, data were obtained from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Data Repository.

Exposure and Outcomes

The primary exposure was baseline serum uric acid concentration, which was measured at baseline in 3,885 of the 3,939 participants. Serum uric acid concentration was determined by standard laboratory procedures using the uricase/peroxidase enzymatic methods (DAX96; Bayer Diagnostics) and measured at the CRIC Central Clinical Laboratory.[31] The outcomes were kidney failure, defined as initiation of dialysis therapy or kidney transplantation, and all-cause mortality. Ascertainment of kidney failure was confirmed by cross-linkage of participants with the US Renal Data System.[28] Participants were followed up until the occurrence of death, voluntary study withdrawal, loss to follow-up, or March 2013.

Covariates

Data obtained at the baseline visit included demographics, detailed medical history, comprehensive medication lists, standardized blood pressure measurements, and anthropometric measurements. History of cardiovascular disease, including coronary artery disease, congestive heart failure, stroke, and peripheral vascular disease, was ascertained by self-report with use of questionnaires administered by study staff at study visits. Blood samples were collected for testing of comprehensive metabolic panels, and urine samples were collected for assessment of urinary albumin-creatinine ratio.[30] We used the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation to calculate eGFR.[32]

Statistical Analysis

Descriptive statistics were summarized as mean ± standard deviation (SD) or median and interquartile range for continuous variables, and frequency distribution is presented with percentages for categorical variables. For skewed data distributions, we performed natural logarithmic transformation as appropriate. We assessed associations between uric acid concentrations and 2-group comparisons using t test and multiple-group comparison using analysis of variance (ANOVA). We used Pearson or Spearman correlations between baseline uric acid concentrations and normally or non-normally distributed laboratory values, respectively. We used χ^2 tests to compare uric acid quartiles with categorical variables, and ANOVA or Kruskal-Wallis tests for normally or non-normally distributed continuous variables, respectively. We evaluated the independent predictors of uric acid concentrations with multivariable linear regression. We also evaluated the correlation between uric acid concentration and measured GFR (mGFR) in a subset of the cohort assessed by using urinary clearance of ^{125}I-iothalamate.[29]

We performed time-to-event analyses to examine the risk for the outcomes, evaluating uric acid concentration as a continuous variable (per 1-SD increase) and as quartiles (lowest quartile as reference group). We used Cox proportional hazards regression to investigate the unadjusted and multivariable-adjusted associations between uric acid concentrations and outcomes. For each outcome of interest, we fitted a series of hierarchically adjusted models: model 1 (unadjusted); model 2 was stratified by site and included age, sex, race, systolic blood pressure, diabetes mellitus, prior cardiovascular disease, smoking status, and body mass index (BMI); model 3 included model 2 and further adjusted for medications (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, statin, antiplatelet agent, urate-lowering medicines, and diuretic) and pertinent laboratory markers (hemoglobin, serum albumin, and natural logarithm–transformed urinary albumin-creatinine ratio); and model 4 included model 3 and further adjusted for baseline eGFR. We examined the possibly nonlinear relation between uric acid concentration and each primary outcome with restricted cubic splines. Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and cubic-spline terms.[33] We tested for statistical interaction between sex, urate-lowering medicines, BMI, and eGFR and uric acid concentrations in Cox models through multiplicative interaction terms. Less than 3.5% of covariate data were missing and therefore we did not use imputation techniques. The proportional hazard assumption was assessed in all models by using the Kolmogorov-type supremum test, and functional forms of the covariates were assessed by checking martingale residuals. Follow-up for the primary analysis was censored at death for the outcomes of kidney failure and all-cause mortality. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc). All statistical tests were 2 sided, and $P < 0.05$ was considered significant.

Sensitivity Analyses

Because the primary analysis censored for death with the outcome of kidney failure and death precludes the ability to reach the outcome of interest, we used subdistribution hazards models in sensitivity analysis.[34] In additional sensitivity analyses for mortality as an outcome, we censored at the onset of kidney failure because the onset of kidney failure may alter the baseline hazard. We also repeated the primary analyses for both outcomes in the subset of participants with mGFR assessed by means of urinary ^{125}I-iothalamate clearance.