Uric Acid and Long-term Outcomes in CKD

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Background: Hyperuricemia is prevalent in patients with chronic kidney disease (CKD); however, data are limited about the relationship of uric acid levels with long-term outcomes in this patient population.

Study Design: Cohort study.

Setting & Participants: The Modification of Diet in Renal Disease (MDRD) Study was a randomized controlled trial (N = 840) conducted from 1989 to 1993 to examine the effects of strict blood pressure control and dietary protein restriction on progression of stages 3 to 4 CKD. This analysis included 838 patients.

Predictor: Uric acid level.

Outcomes & Measurements: The study evaluated the association of baseline uric acid levels with all-cause mortality, cardiovascular disease (CVD) mortality, and kidney failure.

Results: Mean age was 52 ± 12 (SD) years, glomerular filtration rate was 33 ± 12 mL/min/1.73 m^2, and uric acid level was 7.63 ± 1.66 mg/dL. During a median follow-up of 10 years, 208 (25%) participants died of any cause, 127 (15%) died of CVD, and 553 (66%) reached kidney failure. In multivariate models, the highest tertile of uric acid was associated with increased risk of all-cause mortality (hazard ratio [HR], 1.57; 95% confidence interval [CI], 1.07 to 2.32), a trend toward CVD mortality (HR, 1.47; 95% CI, 0.90 to 2.39), and no association with kidney failure (HR, 1.20; 95% CI, 0.95 to 1.51) compared with the lowest tertile. In continuous analyses, a 1-mg/dL greater uric acid level was associated with 17% increased risk of all-cause mortality (HR, 1.17; 95% CI, 1.05 to 1.30) and 16% increased risk of CVD mortality (HR, 1.16; 95% CI, 1.01 to 1.33), but was not associated with kidney failure (HR, 1.02; 95% CI, 0.97 to 1.07).

Limitations: Primary analyses were based on a single measurement of uric acid. Results are generalizable primarily to relatively young white patients with predominantly nondiabetic CKD.

Conclusions: In patients with stages 3 to 4 CKD, hyperuricemia appears to be an independent risk factor for all-cause and CVD mortality, but not kidney failure.

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INDEX WORDS: Kidney disease; uric acid; outcomes; cardiovascular; mortality; kidney failure.

Several,[1-4] but not all,[5-8] studies of the general population have suggested an association between uric acid level and cardiovascular outcomes. Many studies also have shown an association of uric acid level with such established cardiovascular risk factors as hypertension and diabetes.[9-12] Hyperuricemia is highly prevalent in patients with chronic kidney disease (CKD).[13]

Thus, uric acid may have a role as a uremia-related cardiovascular risk factor in patients with CKD. Although 2 studies of patients with kidney failure found a J-shaped association between uric acid level and all-cause mortality,[14,15] this relationship has not been studied in patients in the earlier stages of CKD. It is unclear whether uric acid level is a marker for increased cardiovascu-

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lar disease (CVD) and all-cause mortality in this patient population and whether the relationship between uric acid level and mortality is independent of traditional CVD risk factors.

Given the interrelationship between CVD and progression of CKD,[16] it is possible that uric acid level also is a risk factor for progression of kidney disease. Existing data about this relationship are contradictory. Although a few studies showed that hyperuricemia was associated with progression of kidney disease,[13,17-19] others failed to show this relationship.[20] These studies were limited by imprecise measures of kidney function and lack of data for proteinuria.

Using data from the Modification of Diet in Renal Disease (MDRD) Study randomized cohort, we examined whether uric acid level is an independent risk factor for the development of outcomes during long-term follow-up in patients with predominantly nondiabetic stages 3 to 4 CKD.

METHODS

Participants and Measurements

Details of the MDRD Study have been described previously.[21] The MDRD Study was a randomized controlled trial conducted from 1989 to 1993 that tested the effect of dietary protein restriction and strict blood pressure control on the rate of progression of kidney disease in 840 individuals. Baseline entry criteria included age of 18 to 70 years and serum creatinine level of 1.2 to 7 mg/dL in women and 1.4 to 7 mg/dL in men. Exclusion criteria were pregnancy, type 1 diabetes, insulin-dependent type 2 diabetes, glomerulonephritis caused by autoimmune diseases, obstructive uropathy, renal artery stenosis, proteinuria with protein greater than 10 g/d, mean arterial pressure greater than 125 mm Hg, and prior kidney transplantation. Glomerular filtration rate (GFR) was measured by using iothalamate clearance. In study A (GFR, 25 to 55 mL/min/1.73 m^2), patients were prescribed a usual- or low-protein diet. In study B (GFR 13 to 24 mL/min/1.73 m^2), patients were prescribed 1 of 2 low-protein diets: the same-low protein diet as in study A or a very low-protein diet supplemented with a mixture of keto-acids and amino acids. Studies A and B were combined for the present analysis, which includes 838 patients with baseline uric acid measurements. Uric acid was measured at baseline at the MDRD Study Central Biochemistry Laboratory (Department of Biochemistry, Cleveland Clinic Foundation, Cleveland, OH).

Outcomes

We assessed 3 outcomes: all-cause mortality, CVD mortality, and kidney failure (defined as requirement for dialysis or transplantation). Survival status and cause of death through December 31, 2000, were ascertained by review of death certificates using the National Death Index. A death was ascribed to CVD if the primary cause of death was CVD (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 390 to 459) or kidney disease or diabetes was listed as the primary cause of death and CVD (*ICD-9* codes 390 to 459) was the secondary cause of death. Diabetes was defined as *ICD-9* codes 250.0 to 250.9. Death caused by kidney disease was defined as *ICD-9* codes 580 to 599 and 753.1. Kidney failure outcomes were obtained from the US Renal Data System through December 31, 2000. Data collection procedures were approved by the Cleveland Clinic and Tufts-New England Medical Center Institutional Review Boards.

Statistical Analysis

Distribution and normality of variables of interest were evaluated by using box plots and histograms. Summary statistics by tertiles of uric acid are presented as percentages for categorical data, mean ± SD for approximately normally distributed continuous variables, and median and interquartile range for skewed continuous variables. Differences between uric acid groups were tested by using χ^2 test for categorical variables, analysis of variance for approximately normally distributed continuous variables, and Kruskall Wallis test for skewed continuous variables.

Cox proportional hazards models stratified by study were used to evaluate the relationship between uric acid tertiles and all-cause mortality, CVD mortality, and kidney failure, initially without adjustment and subsequently adjusting for several groups of covariates. Covariates were selected for inclusion in the model for P less than 0.1 in univariate analysis (Table 1). Model 1 adjusted for randomization assignments to protein diets and blood pressure strata, age, and sex. Model 2 adjusted for traditional CVD risk factors, including history of CVD, diabetes, body mass index, and high-density lipoprotein cholesterol level in addition to the variables in model 1; systolic blood pressure was forced into the model given its known association with uric acid level and the outcomes of interest. Model 3 adjusted for variables in model 2 and kidney disease factors: GFR, serum albumin level, and diuretic use, with additional adjustment for cause of kidney disease and log-transformed proteinuria for the kidney failure outcome, and model 4 adjusted for model 3 covariates plus allopurinol use. Proportional hazards assumptions were tested by using log minus log survival plots and plots of Schoenfeld residuals versus survival time.

To maximize statistical power to examine the relationship between uric acid level and mortality, continuous variable analyses were conducted with hazard ratios (HRs) presented per 1-mg/dL greater uric acid level. We performed 2 multivariable models corresponding to the previously described models 3 and 4.

Finally, because high uric acid levels may lead to hypertension and hypertension may be in the causal pathway between uric acid level and the outcomes, fully adjusted models for all-cause and CVD mortality and kidney failure were repeated without adjustment for systolic blood pressure.

Models for the mortality outcomes included patients who developed kidney failure and were censored only at death or the end of follow-up, whereas models for kidney failure were censored at kidney failure, death, or the end of follow-up.