Serum Uric Acid Predicts Progression of Subclinical Coronary Atherosclerosis in Individuals Without Renal Disease

Ticiana C. Rodrigues, MD, PhD1,2 David M. Maahs, MD3 Richard J. Johnson, MD3 Diana I. Jalali, MD

Gregory L. Kinney, MPH1 Christopher Rivard, PhD3 Marian Rewers, MD, MPH, PhD1 Janet K. Snell-Bergeon, PhD1

OBJECTIVE — To examine uric acid (UA) as a possible predictor of the progression of coronary artery calcification (CAC) using data from the prospective Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study.

RESEARCH DESIGN AND METHODS — CAC was measured by electron beam tomography at the baseline and at a follow-up 6.0 ± 0.5 years later. The study population included 443 participants with type 1 diabetes and 526 control subjects who were free of diagnosed coronary artery disease at baseline. The presence of renal disease was defined by the presence of albuminuria and/or low glomerular filtration rate.

RESULTS — In subjects without renal disease, serum UA predicted CAC progression (odds ratio 1.30 [95% CI 1.07–1.58], P = 0.007) independent of conventional cardiovascular risk factors including diabetes and the presence of metabolic syndrome.

CONCLUSIONS — Serum UA levels predict the progression of coronary atherosclerosis and may be useful in identifying who is at risk for vascular disease in the absence of significant chronic kidney disease.

RESEARCH DESIGN AND METHODS — Of the 1,416 individuals asymptomatic for coronary artery disease (CAD) enrolled at baseline, 1,022 had data on coronary artery calcification (CAC) progression. Subjects with coronary events during follow-up (n = 18) and incomplete information about covariates (n = 35) were excluded, resulting in 969 subjects. Clinical and laboratory evaluations were performed as previously described (7). CAC was measured twice and averaged at the baseline and at follow-up 6.0 ± 0.5 years later. CAC progressors were defined as participants whose square root-transformed CAC volume (CVS) increased by ≥2.5 mm (8). Serum UA levels were measured at baseline on the clinical analyzer utilizing a uricase-based commercial kit. Normal albuminuria was defined as overnight albumin excretion rate ≤20 μg/min or urinary albumin-to-creatinine ratio ≤30 mg/g. Glomerular filtration rate (GFR) was estimated by the Mayo Clinic quadratic equation (GFRMC) (9). Metabolic syndrome (MetS) was defined by the original Adult Treatment Panel III (ATP III) criteria (10). The study protocol was approved by the Colorado Combined Institutional Review Board, and informed consent was obtained from all participants.

Statistical analysis
Serum UA, creatinine, cystatin C, and albumin-to-creatinine ratio were log-transformed. We defined normal renal status as a GFRMC ≥60 ml/min per 1.73 m² and normalalbuminuria, and chronic kidney disease (CKD) as GFRMC <60 ml/min per 1.73 m² and/or albuminuria. Stepwise multiple regression analysis was performed to select predictors of CAC progression (Model 1). Renal status was added to this model and interactions between renal status and each variable were tested. SAS 9.2 (SAS Institute, Cary, NC) was used for these analyses.

RESULTS — Subjects with significant progression of CAC (n = 338) were older and had higher CAC at baseline than non-progressors. Serum UA levels were also higher in progressors (5.6 [4.9–6.5 mg/dl]) than in nonprogressors (5.1 [4.4–5.9], P < 0.0001).

Baseline characteristics of participants by renal status are displayed in Table 1. Among subjects with normal renal function, CAC progressed in 263/864 (30%). In subjects with CKD, 75/105 (71.4%) progressed. Age, higher CVS at baseline, and the use of ACE inhibitors or angiotensin receptor blockers were significantly associated with progression. Subjects with CKD had higher UA levels (5.9 [5.1–7.0 mg/dl]) than subjects with normal renal status (5.2 [4.5–6.1], P < 0.0001), and this association was not modified by diabetes status.

In stepwise regression, age, sex, type 1 diabetes, baseline CVS, hypertension,
smoking, HDL cholesterol, LDL cholesterol, and serum UA were retained. Higher baseline serum UA predicted CAC progression (odds ratio [OR] 1.30 for each 1 SD change [0.2 mg], [95% CI 1.07–1.58], P = 0.007).

To explore if UA predicted CAC progression independently of CKD, interaction terms between renal status and all covariates were entered. The effects of sex (P = 0.01 for the interaction), baseline CVS (P = 0.003), and UA (P = 0.01) differed significantly by renal status. In subjects with normal renal status, all variables selected from Model 1 were significantly associated with CAC progression, including UA (OR 1.25 [95% CI 1.01–1.54], P = 0.03). In subjects with CKD, UA was not a predictor of CAC (0.98 [0.55–1.74], P = 0.96). The addition of MetS, alcohol intake, thiazides, ACEs, or angiotensin receptor blockers to the model did not substantially change the results about UA and the outcome.

**CONCLUSIONS** — The novel finding of this study is that UA levels predict CAC progression independently of other established CVD risk factors. In contrast to previous studies associating UA with mortality (3,5), in this report we examined an established marker of coronary plaque burden, allowing for the exploration of early events related to the progression of coronary lesions. Fukui et al. (11) reported an association between higher serum UA and greater intima-media thickness and lower ankle-brachial index in patients with type 2 diabetes. However, this is the first report of an independent association of UA levels on the progression of coronary atherosclerosis.

The only previous study to examine an association between UA and CAD in type 1 diabetes (12) found that hyperuricemia was correlated with the presence of CAD in women but not in men, and that this association was independent of hy-
pertension and nephropathy. Recently published data by our group that show baseline serum UA predicts the development of microalbuminuria after 6 years (13), and Hovind et al. (6) observed that elevated serum UA levels are associated with the development of macroalbuminuria. Rosolowsky et al. (14) reported an association between serum UA and impaired GFR in microalbuminuric and normoalbuminuric type 1 diabetic subjects. Experimental information suggests that UA may mediate the development of both hypertension and renal disease by dysfunction of endothelial and vascular smooth muscle cells resulting in oxidative stress, a reduction in endothelial nitric oxide, and activation of the renin-angiotensin system (15).

We found that UA levels predict CAC progression only in subjects with normal renal function. While UA levels may rise secondary to a fall in GFR, our findings suggest that the temporal relation between the elevation of UA levels and CAC progression is not simply a consequence of declining renal function. As CKD advances, other factors may play a more prominent role in vascular disease such as CKD-associated mineral and bone disorders.

Hyperuricemia is more often seen in people with MetS and has been put forward as one of the criteria of the syndrome (1). Our study demonstrated that UA predicted CAC progression independently of the presence of MetS in subjects without renal disease.

Serum UA level should be considered a marker of increased CAD risk in subjects with and without type 1 diabetes in the absence of significant kidney disease.

Acknowledgments—Support for this study was provided by the National Institutes of Health (NIH); the National Heart, Lung, and Blood Institute grants R01 HL61753, R01 HL68607, and R01 HL079611; and the Diabetes Endocrinology Research Center, Clinical Investigation Core P30 DK57516. The study was performed at the Adult General Clinical Research Center at the University of Colorado Denver Anschutz Medical Center and was supported by the NIH M01 RR00051 at the Barbara Davis Center for Childhood Diabetes in Denver, Colorado, and at the Colorado Heart Imaging Center in Denver, Colorado. T.C.R. was supported by a scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) of the Brazilian government. D.M.M. was supported by K23 DK075360. J.K.S.-B. was supported by the American Diabetes Association-Takeda Cardiovascular Postdoctoral Fellowship 7-09-CVD-06. R.J.J. has several patent applications related to lowering UA as a means to reduce blood pressure or treat MetS. No other potential conflicts of interest relevant to this article were reported.

T.C.R. wrote and edited the manuscript. D.M.M. reviewed and edited the manuscript. R.J.J. reviewed and edited the manuscript. G.L.K. researched the data. M.R. and J.K.S.-B. reviewed and edited the manuscript and contributed to the discussion. D.I.J. and C.R. researched the data. M.R. and J.K.S.-B. reviewed and edited the manuscript and contributed to the discussion.

Parts of this study were presented in abstract form at the 2009 Scientific Sessions of the American Heart Association, Orlando, Florida, 14–18 November 2009.

References

1. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811–1821
2. Sánchez-Lozada LG, Soto V, Tapia E, Avalía-Casado C, Sautin YV, Nakagawa T, Franco M, Rodríguez-Iurbe B, Johnson RJ. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. Am J Physiol Renal Physiol 2008;295:1134–1141
3. Ruggero C, Cherubini A, Miller E 3rd, Maggio M, Najjar SS, Laurentini F, Bandinelli S, Senin U, Ferrucci L. Usefulness of uric acid to predict changes in C-reactive protein and interleukin-6 in 3-year period in Italians aged 21 to 98 years. Am J Cardiol 2007;100:115–121
4. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. JAMA 2000;283:2404–2410
5. Zoppini G, Tarhger G, Negri C, Stoico V, Perrone F, Muggeo M, Bonora E. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care 2009;32:1716–1720
6. Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. Diabetes Care 2009;32:1668–1671
7. Dabelea D, Kinney G, Snell-Bergeon JK, Holkanson JE, Eckel RH, Ehrlich J, Garg S, Hamman RF, Rewers M. Coronary Artery Calcification in Type 1 Diabetes Study. Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. Diabetes 2003;52:2833–2839
8. Holkanson JE, MacKenzie T, Kinney G, Snell-Bergeon JK, Dabelea D, Ehrlich J, Eckel RH, Rewers M. Evaluating changes in coronary artery calcium: an analytic method that accounts for interscan variability. AJR Am J Roentgenol 2004;182:1327–1332
9. Rule AD, Rodeheffer RJ, Larson TS, Burnett JC Jr, Cosio FG, Turner ST, Jacobsen SJ. Limitations of estimating glomerular filtration rate from serum creatinine in the general population. Mayo Clin Proc 2006;81:1427–1434
10. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497
11. Fukui M, Tanaka M, Shiroyahi E, Harusato I, Hosoeda H, Asano M, Kadono M, Hasegawa G, Yoshikawa T, Nakamura N. Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. Metabolism 2008;57:629–629
12. Rathmann W, Hauner H, Dannell H, Gries FA. Association of elevated serum uric acid with coronary heart disease in diabetes mellitus. Diabete Metab 1993;19:153–166
13. Jalal DI, Rivard CJ, Johnson RJ, Maahs DM, McFann K, Rewers M, Snell-Bergeon JK. Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: findings from the Coronary Artery Calcification in Type 1 Diabetes study. Nephrol Dial Transplant 2010;25:1865–1869
14. Rosolowsky ET, Facciolli LH, Maselli NJ, Niewczas MA, Binns AL, Roshan B, Warram JH, Krolevski AS. High-normal serum uric acid is associated with impaired glomerular filtration rate in nonprotein-uric patients with type 1 diabetes. J Am Soc Nephrol 2008;19:706–713
15. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol 2005;16:3553–3562