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

TICIANA C. RODRIGUES, MD, PHD[1,2]
DAVID M. MAAHS, MD[1]
RICHARD J. JOHNSON, MD[3]
DIANA I. JALAL, MD[3]
GREGORY L. KINNEY, MPH[1]
CHRISTOPHER RIVARD, PHD[3]
MARIAN REWERS, MD, MPH, PHD[1]
JANET K. SNELL-BERGEON, PHD[1]

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.

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Elevated serum uric acid (UA) is associated with kidney disease, but it has also been linked to endothelial dysfunction and development of hypertension irrespective of renal involvement (1). UA may contribute to the atherosclerotic process through induction of endothelial dysfunction (2) and inflammation (3).

Serum UA levels have been correlated with negative cardiovascular outcomes in the general population (4) and type 2 diabetic subjects (5) and predict the progression of diabetic nephropathy (6) in type 1 diabetic subjects. The objective of this study was to evaluate UA levels as a predictor of subclinical atherosclerosis progression in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study.

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. Normoalbuminuria 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 m^2 and normoalbuminuria, and chronic kidney disease (CKD) as GFRMC <60 ml/min per 1.73 m^2 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 nonprogressors. 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,

From the [1]Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, Colorado; the [2]Division of Endocrinology, Hospital de Clinicas de Porto Alegre, Rio Grande do Sul, Brazil; and the [3]Division of Renal Diseases and Hypertension, University of Colorado Denver, Aurora, Colorado.
Corresponding author: Janet K. Snell-Bergeon, janet.snell-bergeon@ucdenver.edu.
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Table 1—*Clinical and laboratory characteristics at baseline between progressors and nonprogressors by renal status*

	Normal renal status			Significant CKD		
	Progressors $n = 263$	Nonprogressors $n = 601$	*P*	Progressors $n = 75$	Nonprogressors $n = 30$	*P*
Age (years)	42 ± 8	37 ± 8	<0.0001	41 ± 8	35 ± 8	0.0005
Male (%)	64	38	<0.0001	62	70	0.47
Type 1 diabetes (%)	47	40	0.03	80	63	0.07
Smoking current (%)	12	7	0.03	11	10	0.90
Smoking ever (%)	22	19	0.31	29	20	0.31
Hypertension (%)	24	9	<0.0001	47	31	0.13
Systolic BP (mmHg)	119 ± 13	112 ± 11	<0.0001	122 ± 14	121 ± 14	0.82
Diastolic BP (mmHg)	80 ± 9	76 ± 7	<0.0001	80 ± 10	81 ± 10	0.81
Baseline square root CAC volume	3.5 ± 5.9	0.22 ± 1.0	<0.0001	5.5 ± 9.0	0.9 ± 2.4	0.006
BMI (kg/m^2)	27 ± 4	25 ± 4	<0.0001	26 ± 4	27 ± 4	0.82
Waist circumference (cm)						
Male	96 ± 11	88 ± 10	<0.0001	93 ± 10	91 ± 11	0.56
Female	84 ± 13	78 ± 11	<0.0001	84 ± 14	78 ± 12	0.42
Waist-to-hip ratio						
Male	0.90 ± 0.06	0.86 ± 0.06	<0.0001	0.89 ± 0.05	0.88 ± 0.05	0.30
Female	0.78 ± 0.06	0.76 ± 0.06	0.002	0.79 ± 0.07	0.79 ± 0.07	0.97
Uric acid (mg/dl)						
Male	5.9 (5.2–6.8)	5.8 (5.2–6.4)	0.42	6.2 (5.4–7.3)	6.5 (5.6–7.7)	0.32
Female	4.8 (4.2–5.4)	4.5 (4.0–5.1)	0.01	5.3 (4.6–5.8)	5.0 (4.5–5.9)	0.52
Total cholesterol (mg/dl)	183 ± 36	183 ± 36	0.27	184 ± 35	179 ± 41	0.76
HDL (mg/dl)	49 ± 14	55 ± 16	<0.0001	53 ± 16	49 ± 14	0.29
LDL (mg/dl)	111 ± 32	106 ± 32	0.03	107 ± 30	107 ± 31	0.88
Triglycerides (mg/dl)	105 (73–149)	90 (64–121)	<0.0001	96 (62–138)	107 (71–139)	0.41
A1C (%)						
Type 1 diabetes	7.8 ± 1.1	7.7 ± 1.2	0.85	8.3 ± 1.3	7.9 ± 0.9	0.20
Control subjects	5.6 ± 0.4	5.4 ± 0.3	<0.0001	5.8 ± 0.5	5.4 ± 0.4	0.03
Serum creatinine (mg/dl)	1.1 (1.1–1.3)	1.1 (1.0–1.3)	0.009	1.3 (1.1–1.5)	1.4 (1.2–1.8)	0.18
Cystatin C (mg/l)	0.78 (0.72–0.84)	0.76 (0.69–0.82)	0.007	0.95 (0.79–0.96)	0.92 (0.76–1.03)	0.84
ACR (mg/g creatinine)	4.8 (3.2–6.6)	4.4 (3.2–5.7)	0.03	59.7 (26–179)	51 (15–276)	0.69
ACE inhibitors/ARB use (%)	16	8	0.001	57	20	0.0005
Thiazide diuretic use (%)	5	2.3	0.04	18	3	0.001
Statin use (%)	17	5	<0.0001	25	10	0.08
Alcohol intake positive (%)	79	77	0.86	59	75	0.05
Number of alcohol drinks/month	21 ± 35	15 ± 25	0.02	11 ± 21	11 ± 18	0.90
MetS (%)	18.2	8.3	<0.0001	30.6	13.3	0.06

Data are means ± SD, %, or geometric means (interquartile range). Any alcohol intake is defined as 12 or more drinks during their lifetime. Drinks per month are a combination of standard amounts of beer (12 oz.), wine (3.5 oz.), or hard liquor (1.5 oz.). ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blockers; BP, blood pressure.

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 independent 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.

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T.C.R. wrote and edited the manuscript. D.M.M. reviewed and edited the manuscript. R.J.J. reviewed and edited the manuscript and contributed to the discussion. D.I.J. and C.R. 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.

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