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

Running Title: Uric acid and subclinical coronary atherosclerosis

Ticiana C. Rodrigues, MD, PhD1,2, David M. Maahs, MD1, Richard J. Johnson, MD3, Diana I. Jalal, MD3, Gregory L. Kinney, MPH1, Christopher Rivard, PhD3, Marian Rewers, MD, MPH, PhD1, Janet K. Snell-Bergeon, PhD1

1 Barbara Davis Center for Childhood Diabetes, University of Colorado Denver, Aurora, Colorado, USA.
2 Division of Endocrinology, Hospital de Clinicas de Porto Alegre, RS, Brazil.
3 Division of Renal Diseases and Hypertension, University of Colorado Denver, Aurora, Colorado, USA.

Address all correspondence and requests for reprints to:
Janet K Snell-Bergeon, MPH, PhD
E-mail: Janet.Snell-Bergeon@ucdenver.edu

Submitted 26 May 2010 and accepted 18 August 2010.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Background: To examine uric acid as a possible predictor of progression of coronary artery calcification (CAC), using data from the prospective Coronary Artery Calcification in Type 1 Diabetes Study.

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 controls, free of diagnosed coronary artery disease at baseline. Presence of renal disease was defined by presence of albuminuria and/or low glomerular filtration rate.

Results: In subjects without renal disease, serum uric acid predicted CAC progression [OR: 1.31 (95% CI: 1.06-1.61), p = 0.01], independent of conventional cardiovascular risk factors, including diabetes and the presence of metabolic syndrome.

Conclusion: Serum uric acid levels predict progression of coronary atherosclerosis and may be useful in identifying who are at risk for vascular disease in the absence of significant chronic kidney disease.

Elevated serum uric acid (UA) is associated with kidney disease, but 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 type 2 diabetes subjects (5) and the general population (4) and predict progression of diabetic nephropathy (6) in type 1 diabetes (T1D) 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.

METHODS
Of the 1416 individuals asymptomatic for coronary artery disease (CAD) enrolled at baseline, 1022 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 ≥2.5mm³. Serum UA levels were measured at baseline on the Clinical Analyzer utilizing an Uricase-based commercial kit. Normoalbuminuria was defined as overnight albumin excretion rate ≤ 20 µg/min or urinary albumin to-creatinine ratio ≤30 mg/g (8). Glomerular filtration rate was estimated by the Mayo Clinic quadratic equation (GFRMC) (9). Metabolic syndrome (MetS) was defined by the original 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/Creatinine ratio were log-transformed. We defined normal renal status as a GFRMC ≥60 ml/min per 1.73 m² and normoalbuminuria, and chronic kidney
Uric acid and subclinical coronary atherosclerosis
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, North Carolina) 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 non-progressors (5.1 [4.4-5.9 mg/dl], 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 use of angiotensin-converting enzyme inhibitors (ACEs) or angiotensin receptor blockers (ARBs) 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 mg/dl], p <0.0001) and this association was not modified by diabetes status.

In stepwise regression, age, gender, T1D, baseline CVS, hypertension, smoking, HDL cholesterol, LDL cholesterol and serum UA were retained. Higher baseline serum UA predicted CAC progression (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 the 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 (OR: 0.98, 95% CI 0.55-1.74, p=0.96). Addition of MetS, alcohol intake, thiazides, ACEs or ARBs to the model did not substantially change the results about uric acid and the outcome.

DISCUSSION

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, 4), in this report we examined an established marker of coronary plaque burden, allowing for exploration of early events related to 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 progression of coronary atherosclerosis.

The only previous study to examine an association between UA and CAD in T1D (12) found that hyperuricemia was correlated with the presence of CAD in women, but not in men, and that this association was independent of hypertension and nephropathy. Recently published data by our group that show baseline serum UA predicts the development of microalbuminuria after six 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 micro- and normoalbuminuric T1D subjects. Experimental information suggest that UA may mediate 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 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 the 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 TID, in the absence of significant kidney disease.

**Author contributions:** TCR wrote and edited manuscript, DMM reviewed/edited manuscript, RJJ reviewed/edited manuscript and contributed to discussion, DIJ and CR reviewed/edited manuscript, GK researched data, MR and JKS reviewed/edited manuscript and contributed to discussion.

**ACKNOWLEDGEMENTS**

Support for this study was provided by the National Institutes of Health, NHLBI grants R01 HL61753, R01 HL68607, and R01 HL079611 and 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 supported by the NIH M01 RR000051, at the Barbara Davis Center for Childhood Diabetes in Denver, CO, and at Colorado Heart Imaging Center in Denver, CO. TCR was supported by a scholarship from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) of the Brazilian government. DMM was supported by K23 DK075360. JKS was supported by the ADA-Takeda Cardiovascular Postdoctoral Fellowship 7-09-CVD-06.

**Disclosure:** Dr Johnson has several patent applications related to lowering uric acid as a means to reduce blood pressure or treat metabolic syndrome. The other authors have no relevant conflict of interest to disclose.

**REFERENCES**


Table 1: Clinical and laboratory characteristics at baseline between progressors and non-progressors by renal status.

<table>
<thead>
<tr>
<th></th>
<th>Normal renal status</th>
<th>Significant CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progressors (N = 263)</td>
<td>Non-progressors (N = 601)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 ± 8</td>
<td>37 ± 8</td>
</tr>
<tr>
<td>Male (%)</td>
<td>64</td>
<td>38</td>
</tr>
<tr>
<td>Type 1 diabetes (%)</td>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td>Smoking current (%)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Smoking ever (%)</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>119 ± 13</td>
<td>112 ± 11</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80 ± 9</td>
<td>76 ± 7</td>
</tr>
<tr>
<td>Baseline square root CAC volume</td>
<td>3.5 ± 5.9</td>
<td>0.22 ± 1.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 4</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist/ hip ratio</td>
<td>0.90 ± 0.06</td>
<td>0.86 ± 0.06</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.9 (5.2-6.8)</td>
<td>5.8 (5.2-6.4)</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>185 ± 36</td>
<td>183 ± 36</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>49 ± 14</td>
<td>55 ± 16</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>111 ± 32</td>
<td>106 ± 32</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>105 (73-149)</td>
<td>90 (64-121)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.8 ± 1.1</td>
<td>7.7 ± 1.2</td>
</tr>
<tr>
<td>Controls</td>
<td>5.6 ± 0.4</td>
<td>5.4 ± 0.3</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1 (1.1-1.3)</td>
<td>1.1 (1.0-1.3)</td>
</tr>
<tr>
<td>Cystatin C (mg/l)</td>
<td>0.78 (0.72-0.84)</td>
<td>0.76 (0.69-0.82)</td>
</tr>
<tr>
<td>A/C ratio (mg/g creatinine)</td>
<td>4.8 (3.2-6.6)</td>
<td>4.4 (3.2-3.7)</td>
</tr>
<tr>
<td>ACE inhibitors/ARB use (%)</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Thiazide diuretic use (%)</td>
<td>5</td>
<td>2.3</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Alcohol intake positive (%)</td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td>Number of alcohol drinks/month</td>
<td>21 ± 35</td>
<td>15 ± 25</td>
</tr>
<tr>
<td>Metabolic Syndrome (%)</td>
<td>18.2</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Data are means ± SD, % or geometric means (interquartile range). CKD: chronic kidney disease; BMI: body mass index; BP: blood pressure; CAC: coronary artery calcification; A/C ratio: albumin/creatinine ratio; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers. 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).