Serum Uromodulin Predicts Less Coronary Artery Calcification and Diabetic Kidney Disease Over 12 Years in Adults With Type 1 Diabetes: The CACTI Study

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OBJECTIVE

Novel biomarkers are needed to better predict coronary artery calcification (CAC), a marker of subclinical atherosclerosis, and diabetic kidney disease (DKD) in type 1 diabetes. We evaluated the associations between serum uromodulin (SUMOD [a biomarker associated with anti-inflammatory and renal protective properties]), CAC progression, and DKD development over 12 years.

RESEARCH DESIGN AND METHODS

Participants (*n* = 527, 53% females) in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study were examined during 2002–2004, at a mean age of 39.6 ± 9.0 years and a median duration of diabetes of 24.8 years. Urine albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) determined by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation were measured at baseline and after a mean follow-up period of 12.1 ± 1.5 years. Elevated albumin excretion was defined as ACR ≥30 mg/g, rapid GFR decline (>3 mL/min/1.73 m^2/year), and impaired GFR as eGFR <60 mL/min/1.73 m^2. SUMOD was measured on stored baseline plasma samples (Meso Scale Discovery). CAC was measured using electron beam computed tomography. CAC progression was defined as a change in the square root–transformed CAC volume of ≥2.5.

RESULTS

Higher baseline SUMOD level conferred lower odds of CAC progression (odds ratio 0.68; 95% CI 0.48–0.97), incident elevated albumin excretion (0.37; 0.16–0.86), rapid GFR decline (0.56; 0.35–0.91), and impaired GFR (0.44; 0.24–0.83) per 1 SD increase in SUMOD (68.44 ng/mL) after adjustment for baseline age, sex, systolic blood pressure, LDL cholesterol, and albuminuria/GFR. The addition of SUMOD to models with traditional risk factors also significantly improved the prediction performance for CAC progression and incident DKD.

CONCLUSIONS

Higher baseline SUMOD level predicted lower odds of both CAC progression and incident DKD over 12 years in adults with type 1 diabetes.

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Myocardial infarction from coronary atherosclerosis and diabetic kidney disease (DKD) is a leading causes of mortality in people with type 1 diabetes (1,2). The vascular complications slowly progress and are often unrecognized until symptoms and signs of later disease become evident in the clinical setting. We and others have previously demonstrated that the prevalence and incidence of coronary artery calcification (CAC) (3), a marker of coronary artery disease (CAD), is increased in asymptomatic adults with type 1 diabetes compared with their normoglycemic peers across all age groups (4). The landmark Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study identified type 1 diabetes–specific risk factors for CAD, including age, diabetes duration, HbA_{1c}, and DKD (5). However, traditional risk factors (age, sex, systolic blood pressure [SBP], smoking, lipids) are unable to adequately predict the development of CAD and DKD in adults with type 1 diabetes (5–7). Therefore, novel biomarkers to improve the prediction of CAD and DKD in type 1 diabetes are needed to identify high-risk patients for whom intensified treatment might be beneficial.

Uromodulin (UMOD), or Tamm-Horsfall protein, is produced by thick ascending loop of Henle. It is the most abundant glycoprotein in urine and is also found in blood. Although its anti-inflammatory and renal protective properties in urine have long been known, the systemic function of UMOD remains elusive (8,9). Previous studies (10–12) have shown that lower serum UMOD (SUMOD) level is associated with a decline in kidney function in adults without diabetes. Further, lower SUMOD level has been linked with cardiovascular disease mortality in coronary patients (13,14). Despite what is known in other cohorts, robust epidemiologic data examining the relationship among SUMOD, CAD, and DKD in adults with type 1 diabetes is currently lacking. Accordingly, in this post hoc analysis, our aim was to evaluate whether SUMOD level predicts the progression of CAC and incident DKD over a 12-year period in adults with type 1 diabetes in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study (4).

RESEARCH DESIGN AND METHODS

Study Design

Participants (n = 527, 53% females) in the prospective CACTI study were examined during 2002–2004, at a mean ± SD age of 39.6 ± 9.0 years and a median duration of diabetes of 24.8 years (Q1 = 19.1, Q3 = 32.1 years), and were re-examined 12.1 ± 1.5 years later. Briefly, the CACTI study was conducted to study CAC in asymptomatic adults (age 20–55 years) with type 1 diabetes who have received a diagnosis before 30 years of age, compared with healthy control subjects. The study was approved by the Colorado Multiple Institutional Review Board, and all participants provided informed consent.

Examination Measurements

Physical examination measurements included height, weight, waist and hip circumference, and SBP and diastolic blood pressure (DBP). BMI was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as an SBP ≥140 mmHg, a DBP ≥90 mmHg, or treatment with antihypertensive medication. A fasting blood sample was collected and stored at −80°C until assayed for measurement of cholesterol (total and HDL) and triglyceride levels. LDL cholesterol (LDL-C) was calculated using the Friedewald equation. All subjects were given standardized questionnaires to obtain demographics, medical history, and medication use, as described elsewhere (4).

DKD

Urine albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR), as determined by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation, were measured at the baseline and after a mean follow-up period of 12.1 ± 1.5 years. The CKD-EPI equation is (mL/minute/1.73 m^2) = 141 × min (serum creatinine/k, 1)$^{\alpha}$ × max (serum creatinine/k, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if black), where k is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates minimum serum creatinine/k or 1, and max indicates maximum serum creatinine/k or 1 (15). Elevated albumin excretion was defined as an ACR ≥30 mg/g, a rapid GFR decline ≥3 mL/min/1.73 m^2/year, and impaired GFR as a eGFR <60 mL/min/1.73 m^2.

CAC Measurement

CAC measurements were obtained in duplicate using an ultrafast Imatron C-150XLP electron beam computed tomography scanner (Imatron, South San Francisco, CA), and the two scores were averaged, as previously described (4). Scans were repeated on follow-up, an average of 12.1 ± 1.5 years after the baseline examination. The presence of CAC was defined as a CAC score >0. Progression of CAC was defined as an increase in the volume of CAC of ≥2.5 square root–transformed units.

SUMOD

SUMOD was measured on stored baseline samples using chemiluminescent immunoassay from Meso Scale Discovery (Gaithersburg, MD). The assay has a lower detection limit of 0.03 ng/mL, and the intra-assay and interassay coefficients of variation are 3.1% and 10.5%, respectively.

Statistical Analysis

Analyses were performed in SAS (version 9.4 for Windows; SAS Institute, Cary, NC). Differences between participants with and without type 1 diabetes, and CAC progressors and nonprogressors, were assessed using the χ^2 test for categorical variables and the t test for continuous variables. Descriptive statistics are presented as number, percentage, mean ± SD, or median (25%, 75%), as appropriate. Variables with skewed distributions were natural log-transformed in multivariable models. To examine the associations among SUMOD, incident impaired GFR, incident elevated albumin excretion, rapid GFR decline, and CAC progression, we used univariable and multivariable (adjusting for baseline age, sex, HbA_{1c}, SBP, LDL-C, and ln ACR/eGFR) logistic regression models. We also examined eGFR, ACR, and CAC across tertiles of SUMOD.

Prediction metrics for incident DKD and CAC progression were also investigated with C-statistics, integrated discrimination index (IDI), and category-free net reclassification improvement (NRI). Participants without data at baseline and follow-up were excluded from the analyses. We created two models: model 1, containing standard risk factors

age, sex, HbA_{1c}, SBP, and LDL-C; and model 2, containing the risk factors in model 1 in addition to SUMOD. The C-statistic has been criticized for insensitivities to changes in clinical decisions yielded for information gained (16,17). Therefore, we also used the IDI and category-free NRI. NRI estimates correct changes in clinical classification across risk thresholds (17), and IDI uses probability differences instead of categories (17,18). Event reclassification describes the percentage of events (i.e., CAC progression) correctly reclassified by the addition of SUMOD to model 1 (age, sex, HbA_{1c}, SBP, and LDL-C [ABC risk factors]). Similarly, nonevent reclassification reports the percentage of nonevents (i.e., no CAC progression) correctly reclassified by the addition of SUMOD to model 1. Significance was based on an α level of 0.05.

RESULTS

Participants' characteristics stratified by type 1 diabetes status are presented in Table 1. Participants with type 1 diabetes had lower SUMOD concentrations compared with values in healthy adults (140.45 $\pm$ 68.40 vs. 169.48 $\pm$ 79.96 ng/mL, $P < 0.0001$). Table 2 reports CAC and DKD parameters at baseline and at 4-year and 12-year follow-up. Table 3 summarizes baseline characteristics according to the presence and absence of CAC progression over 12 years in adults with type 1 diabetes. Of 527 participants, 247 had complete CAC data (Table 3). Participants with CAC progression were on average older and had a longer duration of diabetes compared with those without CAC progression. In addition, participants who experienced CAC progression had higher SBP, lower eGFR, and lower SUMOD concentrations (138.00 $\pm$ 69.00 vs. 159.45 $\pm$ 76.29, $P = 0.02$).

Tertiles of SUMOD

We also examined eGFR, ACR, and CAC at baseline and 12 years of follow-up in Supplementary Table 2. Participants in the low SUMOD tertile (<103.33 ng/mL) had lower eGFR, higher ACR, and higher CAC at baseline and follow-up compared with participants in the high SUMOD tertile ($\geq$168.84 ng/mL), and the differences remained significant after multivariable adjustments.

Multivariable Logistic Regression Models

Greater baseline SUMOD conferred lower odds of CAC progression over 12 years (odds ratio [OR] 0.68; 95% CI 0.48–0.97; $P = 0.03$, per 1 SD [68.40 ng/mL] increase in SUMOD) (Supplementary Fig. 1). In a sensitivity analysis, we demonstrated the same protective relationship between greater baseline SUMOD concentration and CAC progression over 4 years (OR 0.67; 95% CI 0.52–0.87; $P = 0.002$). In a sensitivity analysis, we further adjusted for type 1 diabetes duration and the relationship between elevated SUMOD concentration and CAC progression over 4 years (OR 0.67; 95% CI 0.52–0.88; $P = 0.003$) remained significant, but the relationship between elevated SUMOD concentration and CAC progression over 12 years became attenuated (OR 0.70; 95% CI 0.49–1.01; $P = 0.054$). Furthermore, greater SUMOD concentration at baseline also conferred lower odds of incident chronic kidney disease (CKD) (OR 0.44; 95% CI 0.24–0.83; $P = 0.01$), elevated albumin excretion (OR 0.37; 95% CI 0.16–0.86; $P = 0.02$), and rapid GFR decline (OR 0.56; 95% CI 0.35–0.91; $P = 0.02$) after multivariable adjustments (Supplementary Fig. 2). In sensitivity analyses, we further adjusted for type 1 diabetes duration and the relationships among elevated SUMOD concentration (OR 0.44; 95% 0.23–0.84; $P = 0.01$), elevated albumin excretion (OR 0.35; 95% CI 0.15–0.82; $P = 0.02$), and rapid GFR decline (OR 0.57; 95% CI 0.35–0.92; $P = 0.02$).

Prediction Performance Analyses

The addition of SUMOD to model 1 did not improve C-statistics or IDI for CAC progression, rapid GFR decline, and incident elevated albumin excretion (Table 4 and Supplementary Fig. 3). In contrast, the addition of SUMOD to model 1 improved C-statistics (change in the area under the curve [ΔAUC] 0.08 $\pm$ 0.03, $P = 0.01$) for incident CKD. The addition of SUMOD to model 1 did improve IDI for CAC progression, incident elevated albumin excretion, and incident CKD (Table 4). For category-free NRI (Supplementary Table 1), 27% ($P = 0.003$) and 45%

Table 1—Participants' characteristics stratified by type 1 diabetes status

	CACTI participants		
Variables	Type 1 diabetes (n = 527)	Control subjects (n = 597)	P value
Age at baseline (years)	40 $\pm$ 9	42 $\pm$ 9	<0.0001
Sex (female), %	53	48	0.11
Type 1 diabetes duration at baseline (years)	26 $\pm$ 9	—	—
HbA_{1c} at baseline (%)	7.7 $\pm$ 1.2	5.3 $\pm$ 0.5	<0.0001
HbA_{1c} at baseline (mmol/mol)	61 $\pm$ 13	34 $\pm$ 6	<0.0001
BMI at baseline (kg/m^2)	26 $\pm$ 4	26 $\pm$ 5	0.74
SBP at baseline (mmHg)	112 $\pm$ 13	110 $\pm$ 12	0.007
DBP at baseline (mmHg)	74 $\pm$ 9	77 $\pm$ 9	<0.0001
LDL-C at baseline (mg/dL)	2.6 $\pm$ 0.7	3.2 $\pm$ 0.9	<0.0001
ACEI at baseline (yes), %	33.2	4.2	<0.0001
ARB at baseline (yes), %	9.0	0.6	<0.0001
Statins at baseline (yes), %	30.8	8.5	<0.0001
SUMOD (ng/mL)	140.5 $\pm$ 68.4	169.5 $\pm$ 79.9	<0.0001

Data are presented as the mean $\pm$ SD, unless otherwise indicated. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. A P value of <0.05 indicates significance.

Table 2—CAC and CKD parameters at baseline and 4- and 12-year follow-ups

Characteristics	Baseline	4-year follow-up	12-year follow-up
CAC			
CAC (AU)	0 (0–22.8)	1.5 (0–55.6)	8.6 (0–163.0)
CAC >0 (AU)	23.8 (2.4–189.3)	95.0 (2.0–616.0)	98.5 (12.0–718.0)
CAC progression (%)	—	35	49
DKD parameters			
eGFR (mL/min/1.73 m^2)	99 ± 22	—	84 ± 21
Serum creatinine (mg/dL)	0.90 ± 0.52	—	0.97 ± 0.52
Impaired eGFR (%)	5.9	—	10.4
ACR (mg/g)†	11 (9–12)	—	7 (6–8)
Elevated albumin excretion (%)	16.6	—	11.8

Data are presented as the median (25%–75%) and mean ± SD, unless otherwise indicated. AU, Agatston units. †Data are presented as the geometric mean (95% CI).

(P = 0.02) of events were correctly reclassified by the addition of SUMOD to model 1 for CAC progression and rapid GFR decline, respectively. Similarly, the addition of SUMOD to model 1 correctly reclassified nonevents by 24% ($P < 0.0001$) and 26% ($P < 0.0001$), respectively, for incident CKD and incident elevated albumin excretion (Table 4).

CONCLUSIONS

Adults with type 1 diabetes had lower SUMOD concentrations compared with their peers without diabetes, and, within the population with diabetes, higher SUMOD concentrations predicted lower odds of CAC progression and incident DKD over 12 years. In addition, the addition of SUMOD to the American Diabetes Association ABC risk factors improved the prediction metrics of CAC progression and incident DKD. These data suggest that SUMOD holds promise to help stratify risk and predict the development of cardiovascular disease and DKD in adults with type 1 diabetes.

UMOD is exclusively produced in the thick ascending limb of loop of Henle in the kidneys, is the most abundant protein in urine, and is also found in blood (8). Despite its ubiquitous nature, the function of UMOD remains unclear (8). Several mechanisms have been proposed, including the regulation of sodium transport by activating the Na^+, K^+, 2 Cl^- cotransporter NKCC2 and potassium channel ROMK, blood pressure control, and protection against urinary tract infections and kidney stones. SUMOD may also play a role in kidney injury and immune modulation by augmenting cytokine binding and activating Toll-like receptor 4 (19–21). SUMOD concentrations correlate with urinary UMOD excretion, but circulating concentrations of UMOD are much lower (8). SUMOD also correlates with eGFR in patients with CKD (22), and higher SUMOD concentrations have been associated with lower 10-year mortality risk in individuals undergoing coronary angiography independent of eGFR (13).

With the aid of genome-wide association studies, variants in UMOD were linked with risk for CKD and hypertension in the general population (23,24). Moreover, there are rare mutations in UMOD that cause autosomal-dominant tubulointerstitial kidney disease, which leads to CKD, further emphasizing the potential renal protective role for UMOD (25). UMOD gene variants have also been found to be strong genetic determinants of kidney function in adults with type 2 diabetes, and certain UMOD gene variants have been linked with distal tubular dysfunction and macroalbuminuria in adults with type 1 diabetes (26). To our knowledge, however, this is the first report demonstrating that elevated SUMOD concentration confers lower odds of CAC progression, a marker of atherosclerosis, and incident DKD over 12 years in adults with type 1 diabetes. Lower SUMOD concentration has been shown to be associated with impaired regulation of blood pressure and glomerular filtration (9,22). Our participants with CAC progression also had lower SUMOD concentrations and exhibited features of abnormal renal functions, including higher blood pressure, higher albumin excretion, and lower eGFR at both baseline and 12-year follow-up. Therefore, the relationship between low SUMOD concentration and CAC progression may be mediated by DKD (27,28). On the other hand, there are also data suggesting that the relationship between SUMOD concentration and cardiovascular disease may be independent of overt nephropathy, including data from Delgado et al. (13), which demonstrated a strong relationship between SUMOD concentration and cardiovascular mortality risk independent of eGFR in patients undergoing coronary angiography. Furthermore, it has also been proposed that SUMOD concentration may directly play an important role in the pathogenesis of atherosclerosis by suppressing inflammatory and fibrotic pathways (13). Thus, a low SUMOD

Table 3—Baseline characteristics of participants with type 1 diabetes according to CAC progression

	CAC progression		
Characteristics	Yes (n = 121)	No (n = 126)	P value
Age (years)	45 ± 7	35 ± 8	<0.0001
Duration (years)	30 ± 9	22 ± 7	<0.0001
Sex (female), %	46	54	0.35
SBP (mmHg)	115 ± 12	108 ± 11	<0.0001
DBP (mmHg)	74 ± 8	73 ± 8	0.60
HbA_{1c} (%)	7.7 ± 1.3	7.6 ± 1.1	0.50
eGFR by CKD-EPI creatinine equation (mL/min/1.73 m^2)	93 ± 21	107 ± 17	<0.0001
Serum creatinine (mg/dL)	0.90 ± 0.28	0.80 ± 0.20	0.003
ACR (mg/g)	7 (5–13)	5 (3–9)	0.003
LDL-C (mmol/L)	2.6 ± 0.7	2.6 ± 0.8	0.83
SUMOD (ng/mL)	138.0 ± 69.0	159.5 ± 76.3	0.02

N = 247 participants with type 1 diabetes had complete 12-year data and are included in this table. Data are presented as the mean ± SD and median (25%–75%), unless otherwise indicated.

Table 4—C-statistics and IDI prediction performance models

Models	AUC	ΔAUC ± SE	IDI ± SE
CAC progression			
Model 1 (age, sex, HbA_{1c}, SBP, and LDL-C)	0.85	—	—
Model 1 + SUMOD	0.86	—	—
(Model 1 + SUMOD) vs. model 1	—	0.01 ± 0.01, P = 0.14	0.03 ± 0.01, P = 0.003
Incident CKD			
Model 1 (age, sex, HbA_{1c}, SBP, and LDL-C)	0.75	—	—
Model 1 + SUMOD	0.84	—	—
(Model 1 + SUMOD) vs. model 1	—	0.08 ± 0.03, P = 0.01	0.06 ± 0.02, P = 0.02
Incident elevated albumin excretion			
Model 1 (age, sex, HbA_{1c}, SBP, and LDL-C)	0.62	—	—
Model 1 + SUMOD	0.77	—	—
(Model 1 + SUMOD) vs. model 1	—	0.15 ± 0.11, P = 0.16	0.08 ± 0.03, P = 0.001
Rapid GFR decline			
Model 1 (age, sex, HbA_{1c}, SBP, and LDL-C)	0.61	—	—
Model 1 + SUMOD	0.63	—	—
(Model 1 + SUMOD) vs. model 1	—	0.03 ± 0.04, P = 0.51	0.01 ± 0.01, P = 0.12

Model 1 comprises age, sex, HbA_{1c}, SBP, and LDL-C. The individual performance of model 1 and model 1 + SUMOD are presented as the AUC. The difference in AUC ± SEM (ΔAUC ± SE) and IDI ± SEM (IDI ± SE) were used to compare performances between two models.

concentration might represent a risk factor for CAC because of its relationship with DKD progression or through possible systemic actions on immunity and fibrosis, and studies to determine whether it is simply a biomarker or mediator require further investigation. In fact, the atherosclerotic plaques in type 1 diabetes are thought to be more fibrous with greater inflammation compared with type 2 diabetes and the general population (6,29–33). As a consequence, factors such as SUMOD concentration that impact vascular inflammation could be of particular clinical importance in the setting of type 1 diabetes. Whether intensification of glycemic, blood pressure, and lipid control could raise the SUMOD concentrations and impede the development of DKD and CAC progression is unknown.

The strengths of our study include 12-year prospective data, advanced prediction performance analyses with C-statistics, IDI, and category-free NRI. Nevertheless, there are also important limitations worth mentioning. First, SUMOD data were available only for the 2002–2004 visit, as described above. Second, we used estimated rather than measured GFR in this cohort and were therefore more limited around renal function accuracy and precision, especially in patients with eGFR in the elevated range. For CAC measures, we acknowledge that we did not capture CAC density data, which may be more informative than Agatston scores, and that this is a potentially important area for future analysis in patients with type 1 diabetes. We did not demonstrate a significant improvement in C-statistics for CAC progression with the addition of SUMOD to the model with traditional risk factors. It is important to note that the C-statistic is considered potentially insensitive in assessing the impact of adding a new predictor (e.g., SUMOD) to a previous prognostic model when other strong predictors of the outcome are already included into the same model (34). Because the AUC of our original model (model 1) for CAC progression was high at 0.85, it was likely less sensitive to improved prediction with the addition of SUMOD. In contrast, the addition of SUMOD to model 1 did improve IDI for CAC progression.

In conclusion, higher SUMOD concentrations were strongly associated with lower odds of the development of DKD and CAD over 12 years in adults with type 1 diabetes. In clinical practice, SUMOD may aid in risk stratification (i.e., to determine whether patients are at low or high risk of DKD and progression of CAD). Patients with low SUMOD concentrations may further benefit from more aggressive vascular risk factor control (e.g., glycemia, hypertension, and dyslipidemia control). Second, SUMOD concentration may also be used as an enrollment criterion to recruit participants who are at high risk of DKD and CAD progression, thereby potentially enriching the trial with more events. An enriched clinical trial allows for higher probability of observing a statistically significant risk reduction as high-risk participants will likely yield a greater number of events during the trial. Further research is needed to understand the pathogenesis of SUMOD concentration in DKD and CAD, and to correlate changes in SUMOD concentration in response to existing and novel therapies.

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