Journal of Diabetes and Its Complications 33 (2019) 648–650

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Serum uromodulin is associated with urinary albumin excretion in adolescents with type 1 diabetes

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ARTICLE INFO

Article history:
Received 20 February 2019
Received in revised form 27 May 2019
Accepted 28 May 2019
Available online 3 June 2019

Keywords:
Serum uromodulin
Adolescents
Type 1 diabetes
Urinary albumin excretion
Glomerular filtration rate
Arterial stiffness

ABSTRACT

Early diabetic kidney disease (DKD) occurs in adolescents with type 1 diabetes (T1D). Lower serum uromodulin (SUMOD) predicts DKD progression in adults with T1D. In this study, we demonstrate that lower SUMOD is associated with urinary albumin excretion in adolescents with T1D, suggesting a potential relationship between SUMOD and early kidney dysfunction in T1D youth.

1. Introduction

Cardiovascular disease (CVD) and diabetic kidney disease (DKD) remain major contributors to premature mortality in people with type 1 diabetes (T1D). Previous studies have demonstrated a greater burden of subclinical CVD risk markers, including increased arterial stiffness compared to normoglycemic peers in youth with T1D.[1,2] From a renal perspective, estimated glomerular filtration rate (eGFR) is typically preserved or elevated (hyperfiltration) in adolescents with T1D, even though histological changes characteristic of DKD can be present after only 1.5–5 years of disease onset.[3] Therefore, biomarkers are needed to identify disease prior to functional impairment, so therapies to impede DKD initiation and progression can be implemented.

Accordingly, our group recently demonstrated that low serum uromodulin (SUMOD), a urinary glycoprotein produced by thick-ascending loop of Henle (TALH), predicted progression of coronary artery calcification (CAC) and DKD over 12 years of follow-up in adults with T1D.[4] We also found that low baseline SUMOD associated with increased aortic stiffness in adolescents with T1D.[5] These studies suggest that SUMOD has potential as a biomarker for CVD risk prediction in T1D. Yet to our knowledge, no studies have defined the relationship between SUMOD, albumin excretion, eGFR and arterial stiffness in T1D adolescents. Accordingly, we hypothesized that, in T1D adolescents, SUMOD would be associated with urinary albumin excretion and arterial stiffness as observed in T1D adults.

2. Methods

Study participants were included from the Determinants of Macrovascular Disease in Adolescents with T1D study.[6,7] The study design and population have been previously described in detail.[6,8] Briefly, the inclusion criteria relevant to this analysis were ages 12–19 years and T1D for >5 years. Participants were excluded if they had abnormal cardiac anatomy or arrhythmia. One hundred seventy-nine adolescents with T1D and 61 non-diabetic controls who had available serum samples and data on urinary albumin excretion, eGFR, and vascular stiffness were included in the analysis.

Disclosure: The authors have nothing to disclose.

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https://doi.org/10.1016/j.jdiacomp.2019.05.023
1056-8727/

Height and weight were measured using standard methods. After participants laid supine for a minimum of 5 min, blood pressure was measured using a DynaPulse Pathway. As previously described in detail,[6] brachial artery distensibility (BAD) was obtained with a DynaPulse Pathway instrument. Pulse wave velocity was measured in the carotid-femoral segment (cf-PWV) using arterial tonometry (Sphygmocor). Augmentation Index was also collected over the right radial artery and corrected for individual height and heart rate of 75 beats per minute (AIx@HR75). A fasting blood draw was done for serum glucose, HbA1c, creatinine (enzymatic method; Beckman Coulter Inc., Brea, CA), cystatin C, and SUMOD (ELISA; EUROIMMUN, Medizinische Labordiagnostika). The lower detection limit of SUMOD is 2.0 ng/ml and the intra-assay and inter-assay coefficient variation are 1.8–3.2% and 6.6–7.8%, respectively.

Urinary albumin-creatinine ratio (UACR) and eGFR were used as markers of kidney function. eGFR was estimated by Zappitelli using serum creatinine and cystatin C.[9] The spot urine samples were collected during the study visit and UACR was measured in duplicate. Albuminuria was measured using double-antibody radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA) in duplicate.

Analyses were performed in SAS (version 9.4). Descriptive statistics are presented as mean ± SD or median (Q1, Q3). Student *t*-tests and Chi-square tests were used to compare the means between groups. Skewed data were log-transformed prior to testing. Multivariable regression models were fit to estimate associations between SUMOD, markers of vascular stiffness and kidney function. We employed multivariate models to control for confounders, including age, sex, BMI, SBP, CRP, eGFR and HbA1c. Confounders were selected based on prior data supporting their roles as cardio-renal risk factors in T1D. *p*-Values <0.05 were considered significant.

3. Results

Patient demographics, biochemical characteristics and measures of arterial stiffness and kidney function are shown in Table 1. Adolescents with T1D had lower BAD ($p = 0.02$) but there was no difference in cf-PWV nor AIx@HR75. Youth with T1D also had higher eGFR ($p = 0.001$), whereas UACR was similar between groups. Adolescents with T1D had significantly lower SUMOD compared to controls (150.9 ± 74.2 vs. 178.2 ± 76.0 ng/ml, $p = 0.02$). SUMOD was inversely associated with UACR and eGFR and the relationship between SUMOD and UACR remained significant after adjusting for age, sex, BMI, SBP, eGFR and CRP (β ± SE: −0.002 ± 0.001, $p = 0.036$). However, the association was attenuated after further adjusting for HbA1c (−0.001 ± 0.001, $p = 0.18$). Significant relationships between SUMOD and vascular stiffness were not found (Supplemental Table 1). In nondiabetic controls, SUMOD did not associate with vascular stiffness, eGFR or UACR (Supplemental Table 1).

Table 1
Patient demographic, biochemical characteristics and vascular stiffness measures.

Variables	Type 1 diabetes $N = 179$	Controls $N = 61$	*p*-Value
Age (years)	15.2 ± 2.2	15.4 ± 2.2	0.46
Sex (% male)	38	43	0.55
Ethnic (%non-Hispanic White)	82%	64%	0.12
Diabetes duration (years)	8.6 ± 2.8	–	–
BMI percentile	68.7 ± 23.1	55.7 ± 27.7	0.002
SBP (mmHg)	113 ± 8	107 ± 8	<0.001
DBP (mmHg)	69 ± 6	64 ± 6	<0.001
cf-PWV (m/s)	5.2 ± 0.7	5.2 ± 0.6	0.37
BAD (%/mm Hg)	6.8 ± 13	7.3 ± 1.2	0.02
AIx@ HR75 (%)	3.6 ± 8.8	1.3 ± 9.9	0.15
HbA1c (%)	8.9 ± 1.5	5.3 ± 0.3	<0.001
UACR (mg/g)	7.1 (4.5, 12.4)	7.6 (4.1, 17.1)	0.33
eGFR (ml/min/1.73 m^2)	121 ± 23	112 ± 16	0.001
Serum uromodulin (ng/ml)	150.9 ± 74.2	178.2 ± 76.0	0.02

Data are presented as mean ± SD, median (min-max) and median (Q1, Q3). *p*-Value <0.05 indicates statistical significance.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; cf-PWV, carotid-femoral pulse wave velocity; BAD, brachial artery distensibility; AIx@HR75, augmentation index at heart rate of 75 beats per minute; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

4. Discussion

Subclinical micro- and macrovascular complications are prevalent in adolescents with T1D.[1,10] Identifying people at risk in the early stage of disease is critical to prevent diabetic complications. To our knowledge, we are the first to show that adolescents with T1D have lower SUMOD concentrations than their non-diabetic peers. Further, SUMOD associated with urinary albumin excretion independent of age, sex, BMI, SBP, eGFR and CRP, which is consistent with our data in adults with T1D.[4] However, this association was attenuated after further adjusting for HbA1c despite no significant correlation between SUMOD and HbA1c.

SUMOD levels are consistently lower in people with T1D compared to non-diabetic controls irrespective of age or diabetic duration.[4,5] In contrast to urine uromodulin, SUMOD exhibits more stability; therefore, it is thought to be more reproducible.[11] The mechanism underlying decreased SUMOD in T1D remains unclear. Several studies have shown that urinary uromodulin is initially normal after diabetes diagnosis, increases according to diabetes duration and declines in those with longstanding diabetes (>15 years) or advanced DKD.[12,13] These data implicate an alteration in uromodulin excretion rather than a decreased renal tubular mass which may, in part, explain the lower SUMOD concentrations in people with T1D. SUMOD is proposed to reflect intact tubular mass and SUMOD concentrations decline progressively in several structural and functional renal abnormalities.[11,14]

Beyond reflecting abnormalities in tubular mass, lower circulating uromodulin in T1D adolescents may also indicate that tubulointerstitial dysfunction is involved in the pathogenesis of kidney dysfunction. Several studies have found that uromodulin excretion is increased in the urine of adult T1D participants in the early course of diabetes (duration <15 years).[12,13,15] Yet, limited data exist describing SUMOD concentrations in T1D adolescents. Our results demonstrated that, despite T1D youth had similar UACR compared to controls, only T1D youth exhibited the inverse association between SUMOD and UACR. Even with subtle albuminuria (UACR <10 mg/g), people with T1D are 2.2 times more likely to have CAC progression compared to non-diabetic subjects.[16] Further, the relationship between incident CVD and low-grade UACR (7.4–30 mg/g) is also present in non-diabetic population.[17] Although adolescents with T1D exhibited significantly lower BAD, we did not find any significant associations between SUMOD and measures for arterial stiffness including BAD and cf-PWV. In our previous work, we found that SUMOD was associated with ascending aortic PWV quantified by MRI.[5] The mechanisms explaining the discrepancy between these relationships remain unclear, but may relate to non-uniformed development of atherosclerosis. Previous studies have shown that people with CVD have preferential stiffening in central over peripheral vasculature.[18]

Our study has limitations. The relatively small number of participants may have limited meaningful analyses. Moreover, our study population of fairly well controlled adolescents with T1D without clinical evidence of CVD and DKD, may have reduced our power to detect an association between SUMOD and markers of vascular stiffness and kidney dysfunction in T1D youth.

In summary, our study demonstrated that T1D adolescents have lower SUMOD concentrations compared to their non-diabetic peers, and that low SUMOD concentrations associated with elevated UACR, independent of eGFR. These findings are consistent with adult T1D data and may support the use of SUMOD as a biomarker of kidney function.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2019.05.023.

Funding

Support for this study was provided by NIDDK grants (DK116720, DK075360), JDRF (11-2007-694) and CTSI UL-1 RR025780. The study was performed at the Barbara Davis Center for Childhood Diabetes, Aurora, CO. Dr. Maahs was supported by a grant from NIDDK (DK075360) and (P30DK116074), Dr. Snell-Bergeon by an American Diabetes Association Junior Faculty Award (1-10-JF-50) and Dr. Wadwa by an early career award from the Juvenile Diabetes Research Foundation (11-2007-694). The authors have no financial relationships relevant to this article to disclose. P.B. receives salary and research support by NIH/NIDDK (K23 DK116720-01), in addition to research support by Thrasher Research Fund, Juvenile Diabetes Research Foundation (JDRF), International Society for Pediatric and Adolescent Diabetes (ISPAD), NIH/NIDDK DiaComp, Colorado Clinical and Translational Sciences Institute (CCTSI), Children's Hospital Colorado Research Institute and Center for Women's Health Research at University of Colorado.

Author contributions

P.W. interpreted the data, wrote and edited the manuscript; P.B. formulated analytic plan, reviewed and edited the manuscript; R.J.J., C.R., D.Z.C., and L.P. edited the manuscript; T.R. and F.B. researched data and edited the manuscript; D.M.M. and R.P.W. researched data, formulated analytic plan, reviewed and edited the manuscript.

Acknowledgements

Special thanks to the Determinants of Macrovascular Disease in Adolescents with T1D study and the research participants.

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