Journal of Diabetes and Its Complications 33 (2019) 434–436

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Serum uromodulin inversely associates with aortic stiffness in youth with type 1 diabetes: A brief report from EMERALD study☆,☆☆

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ARTICLE INFO

Article history:
Received 19 October 2018
Received in revised form 5 March 2019
Accepted 16 March 2019
Available online 21 March 2019

Keywords:
Serum uromodulin
Adolescents
Type 1 diabetes
Aortic stiffness
Ascending aortic pulse wave velocity
Relative area change

ABSTRACT

Youth with type 1 diabetes (T1D) carry greater cardiovascular disease (CVD) risk than their nondiabetic peers. Low serum uromodulin (SUMOD) associates with increased CVD mortality in adults. We found that T1D youth have low SUMOD. Lower SUMOD correlated with aortic stiffness, suggesting its potential as a CVD biomarker in T1D.

1. Introduction

Population-based studies suggest that cardiovascular disease (CVD) occurs in ≈ 40% of adults with type 1 diabetes (T1D) over age 65 years.[1] Youth with T1D are already at greater CVD risk compared with their healthy peers,[2,3] as demonstrated by previous studies including our Effects of MEtformin on cardiovasculaR function in AdoLescents with t1D (EMERALD) study showing arterial stiffness in T1D youth.[4–7] Arterial stiffness is a strong predictor of atherosclerosis and CVD mortality,[8] emphasizing the need for biomarkers to identify the early, potentially reversible stages of CVD.

Uromodulin is produced from the thick-ascending loop of Henle. Its physiologic functions include sodium and uric acid excretion, and antibacterial and immunomodulatory properties.[9] Serum uromodulin (SUMOD) is a well-known renal biomarker as the concentrations are age-independent but decline with impaired kidney function from various etiologies.[10] Recently, an association between SUMOD and CVD mortality was reported.[11,12] Our group also identified an inverse relationship between SUMOD and progression of coronary artery calcification (CAC; a marker of atherosclerosis), and incident diabetic kidney disease (DKD) in T1D adults.[13,14] However, the role of SUMOD in initial CVD and DKD development was unknown. Accordingly, we sought to evaluate the association between SUMOD and early markers of aortic stiffness and DKD in T1D adolescents.

2. Methods

Forty-nine T1D adolescents were enrolled in EMERALD study as previously described.[7] Briefly, EMERALD study included T1D adolescents meeting the following inclusion criteria: ages 12–21 years, Tanner stage >1,

☆ Funding: This project was supported by the following: National Center for Research Resources [K23 RR020038-01, R56 DK088971]; American Diabetes Association [ADA 7-11-CD-08, ADA 1-11-JF-23]; JDRF [Award #11-2010-343]; NIH [K23DK116720, BIRCWH K12 5K12HD057022, K23DK107871]; NIH/NCATS Colorado [CTSI UL1 TR001082]; Center for Women's Health Research; VA Merit and Euroimmun (Uromodulin ELISA Kits Supply). Its contents are the authors' sole responsibility and do not necessarily represent official NIH views.
☆☆ Disclosure: The authors have nothing to disclose.
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https://doi.org/10.1016/j.jdiacomp.2019.03.001
1056-8727/

diabetes duration ≥1 year, blood pressure (BP) <140/90 mm Hg, HbA1c <11%, non-smoking, weight < 300 lbs. and no medications affecting BP or insulin sensitivity. Eligible participants were randomized to 3 months of metformin (2000 mg) or placebo, before and after which physical, biochemical and MRI measurements were performed.

Participants' height, weight and BP were measured using standardized procedures. After 12 h of overnight fasting, participants' blood was drawn for HbA1c, creatinine, cystatin C, total cholesterol, LDL, HDL and triglycerides and urine samples were collected for microalbumin and creatinine (enzymatic assays; Beckman Coulter). GFR was estimated (eGFR) by the Zappitelli combined creatinine-cystatin C equation. SUMOD was analyzed using enzyme-linked immunoassay (EUROIMMUN; Medizinische Labordiagnostika) with a lower detection limit of 2.0 ng/mL. Intra-assay and inter-assay coefficient variations were 1.8–3.2% and 6.6–7.8%, respectively.

A gradient echo ECG-gated MRI sequence obtained tissue intensity and phase velocity maps using a 3.0-Tesla magnet (Philips Ingenia, Philips Medical Systems, Netherlands). Aortic stiffness was measured by pulse wave velocity (PWV) using the flow-area method and by computing relative area change (RAC) for the ascending and descending aorta (AA and DA).[7]

Analyses were performed in SAS (version 9.4). Participants were stratified by SUMOD tertiles. *t*-tests were used to compare groups. Differences between baseline and 3-month variables were tested using repeated measures analysis of variance. Correlations were evaluated using Pearson's method. Stepwise multivariable regression models were fit to estimate associations between baseline SUMOD and PWV and RAC in the AA and DA at baseline and 3 months. We also tested the effect of age, sex, BMI, diabetes duration, urinary albumin concentrations, eGFR and treatment group (metformin or placebo) on the regression models. *P*-values <0.05 were considered significant.

3. Results

Table 1 displays the participant characteristics, fasting biochemical and aortic stiffness data. SUMOD and BP were not significantly correlated. SUMOD positively correlated with AA-RAC ($r = 0.370$, $p = 0.04$) and negatively with AA-PWV ($r = -0.410$, $p = 0.03$) at baseline but not in regression models. Participants in the low SUMOD tertile had significantly higher AA-PWV than the mid- and high-tertiles (Fig. 1). In multivariable linear regression models, baseline SUMOD was inversely associated with AA-PWV over 3 months [β (95% CI): -0.039 (CI -0.017 to -0.062), $p = 0.007$], adjusting for age, sex, BMI, HbA1C, diabetes duration, baseline AA-PWV and treatment group. The relationship remained significant after further adjustment for eGFR and microalbuminuria [β (95% CI): -0.018 (−0.034 to −0.002), $p = 0.045$]. Similar relationships were not observed for the DA.

4. Discussion

We demonstrated for the first time that low SUMOD is associated with aortic stiffness in T1D adolescents. Moreover, SUMOD concentrations in our T1D youth were lower than previously reported in healthy

Table 1
Participant characteristics.

Variables	Type 1 diabetes ($n = 49$)		P-value	Adjusted *p*-value
	Baseline	3 months		
Age (years)	16.6 ± 2.6	16.9 ± 2.5	–	–
Diabetes duration (years)	7.9 ± 4.0	8.2 ± 4.0	–	–
Female, N (%)	25 (51%)	–	–	–
Ethnicity, N (%)				
Hon-Hispanic White	42 (86%)	–		
Hispanic	4 (8%)	–	–	–
Non-Hispanic Black	1 (2%)	–		
American Indian	2 (4%)	–		
Pubertal stage	5 (4, 5)	5 (4, 5)	0.32	–
Body weight (kg)	70.4 ± 14.0	73.4 ± 13.5	0.12	0.003
Body mass index, BMI (kg/m^2)	25.2 ± 4.6	25.6 ± 4.5	0.23	0.005
BMI percentile	83.6 (63, 95)	83.0 (70, 93)	0.12	0.01
Waist Circumference (cm)	79.5 ± 13.0	79.1 ± 10.3	0.61	0.53
Systolic blood pressure (mm Hg)	121 ± 9	114 ± 12	0.89	0.37
Diastolic blood pressure (mm Hg)	71 ± 8	60 ± 11	0.26	0.65
Insulin delivery method, N (%)				
Insulin pump	39 (80%)	–	–	–
Multiple daily injection	10 (20%)	–		
Total daily insulin dose/kg (units/kg)	0.9 ± 0.2	0.8 ± 0.3	0.05	0.53
HbA1c (%)	8.6 ± 1.4	8.7 ± 1.6	0.99	0.88
Serum uromodulin (ng/mL)	114.5 ± 62.2	–	–	–
Serum creatinine (Cr, mg/dL)	0.73 ± 0.14	0.76 ± 0.16	0.09	0.04
Serum cystatin-C (mg/L)	0.82 ± 0.13	0.91 ± 0.13	0.49	0.15
Urine microalbumin:Cr ratio (mg/g)	8.0 (4.5, 33)	7.4 (4.2, 21)	0.13	0.66
eGFR by Zappitelli (ml/min/1.73m^2)	102 ± 18	103 ± 20	0.14	0.16
Total cholesterol (mg/dL)	146 ± 27	139 ± 20	0.75	0.42
LDL (mg/dL)	84 ± 19	81 ± 19	0.82	0.30
HDL (mg/dL)	44 (39, 51)	43 (39, 52)	0.83	0.93
Triglycerides (mg/dL)	74 (53, 96)	75 (56, 97)	0.13	0.98
hs-CRP (mg/L)	0.9 (0.3, 3)	0.8 (0.3, 4)	0.26	0.21
AA-PWV (m/s)	3.6 ± 1.9	4.0 ± 3.4	0.33	0.34
DA-PWV (m/s)	4.2 ± 1.5	3.7 ± 0.6	0.92	0.66
AA-RAC (%)	26.7 ± 5.0	26.3 ± 7.9	0.45	0.36
DA RAC (%)	22.3 ± 4.5	27.0 ± 6.8	0.004	0.76

Data are presented as mean ± SD, and median (Q1, Q3).
P-values were calculated using repeated measures ANOVA. Adjusted p-values were analyzed using one-way repeated measures ANOVA with analysis of covariance adjusting for treatment group (metformin or placebo).
eGFR, estimated glomerular filtration rate; AA, ascending aorta; DA, descending aorta; PWV, pulse wave velocity; RAC, relative area change.

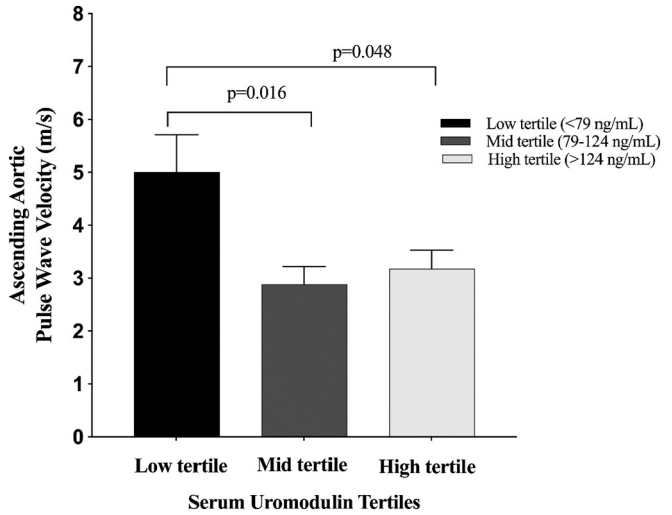

Fig. 1. Ascending aortic pulse wave velocity according to serum uromodulin concentration tertiles. Data are presented as bar graphs. The black, dark gray and light gray bars indicate mean ascending aortic pulse wave velocities in participants in the low, mid and high tertiles of serum uromodulin concentrations, respectively. The error bars represent standard error of the mean (SEM).

adolescents.[10] Prior T1D papers have utilized urine uromodulin (UUMOD),[15,16] yet it is unclear whether UUMOD concentrations reflect SUMOD, as the function and transport of uromodulin remains elusive.[17] A study of newly-diagnosed T1D youth reported persistently decreased UUMOD despite good metabolic control and normal albumin excretion during follow-up.[15] Another study found that patients with T1D duration ≥10 years had elevated UUMOD, a finding attributed to renal hyperfiltration.[16]

We found that low SUMOD related to greater aortic stiffness at baseline and 3 months of follow-up, independent of treatment group. This association was found only in the ascending aorta, the most sensitive aortic region for hemodynamic-flow shear stress-induced early vascular remodeling.[18] Consistent with these findings, we demonstrated that lower SUMOD conferred greater odds of CAC progression over 12 years in T1D adults[14] and Delgado reported in 3057 participants with and without diabetes referred for angiography that lower SUMOD related to overall and CVD mortality.[11]

The pathophysiology underlying low SUMOD and aortic stiffness remains unclear. Uromodulin is exclusively produced by the kidney and thought to reflect nephropathy, in addition to serving biological roles in renal and systemic immunomodulation and fibrosis.[19] We also previously reported that lower SUMOD predicted higher rates of DKD progression, a well-known CVD risk factor, in T1D adults.[14] Taken together, the relationship between SUMOD and CVD might be renally-mediated. However, in our study, the relationship between SUMOD and aortic stiffness was independent of eGFR. Indeed, Delgado et al. showed similarly that SUMOD related to CVD mortality irrespective of eGFR, potentially implicating other mechanisms.[11] The same study also demonstrated that SUMOD inversely related to serum inflammatory and fibrotic markers, which may contribute to atherosclerosis.

Our study has limitations. AA-PWV is a surrogate marker of CVD, and as such the relationship between SUMOD and AA-PWV may not represent actual CVD risk. Second, GFR estimating equations have suboptimal accuracy at the normal-to-elevated GFR ranges seen in adolescents, which may have impaired our ability to identify a relationship between SUMOD and eGFR.

In conclusion, lower SUMOD in adolescents with T1D is associated with aortic stiffness at baseline and over 3-months of follow-up. Further studies are needed to differentiate whether SUMOD is simply a biomarker or has a biological role in CVD in T1D.

Author contributions

P.W. researched data, performed data analysis, wrote and edited the manuscript, P.B. formulated analytic plan, reviewed and edited the manuscript, M.C.G. edited the manuscript, AB researched data and edited the manuscript, G.C. edited the manuscript, Y.G.R. researched data and edited the manuscript, M.S. edited the manuscript, UT created the MRI protocol and oversaw MRI image quality, as well as edited the manuscript, L.P. edited the manuscript; J.G.R. edited the manuscript; K.J.N. researched data, formulated analytic plan, reviewed and edited the manuscript.

Acknowledgements

Special thanks to the EMERALD Study Group and the research participants. This project was supported by the following: NCRR [K23-RR020038-01, R56-DK088971]; ADA [ADA 7-11-CD-08, ADA 1-11-JF-23]; JDRF [Award #11-2010-343]; NIH [K23-DK116720, BIRCWH-K12-5K12HD057022, K23-DK107871]; NIH/NCATS [Colorado CTSI UL1 TR001082]; Center for Women's Health Research; and VA Merit and Euroimmun (Uromodulin ELISA Kits Supply). Its contents are the authors' sole responsibility and do not necessarily represent official NIH views. None of the authors have any conflicts of interest to disclose.

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