



Association Between Plasma Uric Acid Levels and Cardiorenal Function in Adolescents With Type 1 Diabetes

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Yuliya Lytvyn,^{1,2} Farid H. Mahmud,³
 Denis Daneman,³ Livia Deda,³
 David B. Dunger,⁴ John Deanfield,⁵
 R. Neil Dalton,⁶ Yesmino Elia,³
 Ronnie Har,² Timothy J. Bradley,⁷
 Cameron Slorach,⁷ Wei Hui,⁷
 Rahim Moineddin,⁸ Heather N. Reich,²
 James W. Scholey,² Luc Mertens,⁷
 Etienne Sochett,³ and David Z.I. Cherney²

OBJECTIVE

The relationship between plasma uric acid (PUA) and renal and cardiovascular parameters in adolescents with type 1 diabetes (T1D) is not well understood. Our aims in this exploratory analysis were to study the association between PUA and estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (ACR), blood pressure, endothelial function, and arterial stiffness in T1D adolescents. These associations were also studied in healthy control (HC) subjects.

RESEARCH DESIGN AND METHODS

We studied 188 T1D subjects recruited to the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) and 65 HC subjects. Baseline PUA, eGFR_{cystatin C}, ACR, blood pressure, flow-mediated dilation (FMD), and carotid-femoral pulse wave velocity (PWV) were measured.

RESULTS

PUA was lower in T1D vs. HC subjects (242 ± 55 vs. 306 ± 74 $\mu\text{mol/L}$, respectively; $P < 0.0001$). Higher PUA was inversely associated with eGFR in T1D subjects ($r = -0.48$, $P < 0.0001$) even after correction for baseline clinical demographic characteristics. PUA was not associated with ACR in T1D after adjustment for potential confounders such as eGFR. For cardiovascular parameters, PUA levels did not associate with SBP, FMD, or PWV in T1D or HC subjects.

CONCLUSIONS

Even within the physiological range, PUA levels were significantly lower in T1D adolescent patients compared with HC subjects. There was an inverse relationship between PUA and eGFR in T1D, likely reflecting an increase in clearance. There were no associations observed with ACR, blood pressure, arterial stiffness, or endothelial function. Thus, in contrast with adults, in adolescents with T1D PUA may not yet be associated with cardiorenal abnormalities.

Recent evidence from animal and human models suggests that plasma uric acid (PUA) levels are associated with multiple key pathways implicated in the pathogenesis of type 1 diabetes (T1D) complications, such as metabolic abnormalities (insulin resistance and hyperglycemia), cardiovascular disease (hypertension, endothelial dysfunction, arterial stiffness, and cardiac diastolic dysfunction) and kidney dysfunction (1). In healthy adult men and women, PUA is positively associated with activation of proinflammatory pathways and activation of the renin-angiotensin-aldosterone

¹Department of Pharmacology, University of Toronto, ON, Canada

²Division of Nephrology, Department of Medicine, University Health Network, University of Toronto, Toronto, Canada

³Division of Endocrinology, Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON Canada, JDRF Canadian Clinical Trial Network SickKids Multicenter Clinical Trial Center

⁴Department of Pediatrics, University of Cambridge, Cambridge, U.K.

⁵University College Hospital, London, U.K.

⁶WellChild Laboratory, Evelina Children's Hospital, St Thomas' Hospital, London, U.K.

⁷Division of Cardiology, Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada

⁸Department of Family and Community Medicine, University of Toronto, Toronto, Canada

Corresponding author: David Z.I. Cherney, david.cherney@uhn.ca.

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system (RAAS) (1). Perhaps as a consequence of PUA-mediated inflammation and RAAS activation, PUA levels—even within the normal range—are independently associated with endothelial dysfunction, arterial stiffness, impaired renal function, and albuminuria in adults with T1D and in the general adult population (1). Consequently, the potential renal and vascular protective effects of PUA lowering are being investigated in a T1D population with microalbuminuria in the Protecting Early Renal Function Loss (PERL) study (clinical trial reg. no. NCT02017171, clinicaltrials.gov) (2).

In adolescents, elevated PUA levels have also been linked with metabolic syndrome (3,4), obesity, cardiovascular risk (5), inflammation (6), pediatric hypertension, and the subsequent development of hypertension in adulthood (1). Similar to observations by others, we also recently showed that PUA levels are lower in otherwise healthy adult T1D patients between 18 and 35 years of age compared with healthy control (HC) subjects (7). This may be due to a decrease in uric acid reabsorption mediated by high concentrations of glucose in the tubular lumen (7). Despite lower PUA levels in adults with T1D, PUA negatively correlates with estimated glomerular filtration rate (eGFR) and effective renal plasma flow (7,8). The association between higher PUA with lower glomerular filtration rate and effective renal plasma flow may be on the basis of PUA-mediated renal vasoconstriction (7,8). PUA levels have not yet been characterized in an even earlier, subclinical disease population, such as in adolescent patients with T1D. Establishing the relationship between PUA and early markers of renal and cardiovascular risk in T1D patients is important to potentially identify predictors of future complications and to target new interventions aimed at improving long-term prognosis.

Accordingly, the goal of this exploratory analysis was to assess the relationship between PUA and important physiologic parameters in patients with early T1D (9). The associations between PUA, eGFR, flow-mediated dilation (FMD) (measure of endothelial function) and vascular stiffness measures were assessed in T1D and compared with those in HC adolescents.

Based on the above observations in adults, we hypothesized that the T1D adolescent cohort would exhibit lower PUA overall and that higher PUA, even within the normal range, would be associated with higher blood pressure, lower eGFR, higher urinary albumin excretion, impaired FMD, and increased arterial stiffness measures in the adolescent T1D cohort but not in HC.

RESEARCH DESIGN AND METHODS

Subject Inclusion Criteria and Study Preparation

All studies were approved by The Hospital for Sick Children Research Ethics Board. All study participants provided assent, and parents signed the informed consent documents. This analysis was conducted using the blood and urine samples collected from 188 T1D subjects from the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) (9) and 65 HC. We included 11- to 16-year-old adolescents who achieved a minimum of Tanner stage 2 for puberty and were not taking medication that could interfere with the RAAS. The albumin-to-creatinine ratio (ACR) measures were obtained by taking two sets of three consecutive early-morning urine samples on two separate visits, and the average ACR was calculated and adjusted on a log ACR scale using age, diabetes duration, sex, and the coefficients from the Oxford Regional Prospective Study (ORPS) linear regression model (9–11). In AdDIT, the T1D participants were divided into the following ACR tertiles: 1) 64 patients in the low ACR tertile (<0.8 mg/mmol), 2) 74 patients in the middle ACR tertile (0.8–1.2 mg/mmol), and 3) 50 patients in the high ACR tertile (>1.2 mg/mmol). The tertile boundaries were determined based on preliminary data from the ORPS cohort, which predicted the risk for development of microalbuminuria (10).

Renal Assessments

All urine and blood samples were obtained during the screening phase of the study. eGFR was calculated using the Larsson formula: $eGFR = 77.24 \times \text{cystatin C}^{-1.2623}$, where cystatin C was measured by laser immunonephelometry (Dade Behring) (12,13). As in our previous work, T1D adolescent participants

were also subdivided into a normofiltration and a hyperfiltration group, where hyperfiltration was defined as $eGFR \geq 135$ mL/min/1.73 m² (14–17).

Vascular Assessments, Sample Collection, and Analytical Methods

Arterial stiffness was measured using a SphygmoCor device (SphygmoCor, AtCor Medical Systems, Sydney, Australia). A high-fidelity micromanometer was used to record right radial, carotid, and femoral artery pulse pressure waveforms. The corresponding central aortic pressure waveform was generated using a validated transfer function. Mean arterial pressure and heart rate was determined by the analysis software. The distance between the carotid-femoral pulse points was measured and pulse time delay was calculated to obtain pulse wave velocity (PWV).

Endothelial function of the brachial artery was determined by FMD. A pneumatic cuff was placed distal of the antecubital fossa. Reactive hyperemia was stimulated by a 5-min inflation of the cuff followed by deflation. A high-resolution B-mode ultrasound was used to capture longitudinal electrocardiogram-gated end-diastolic images of the brachial artery pre- and post-cuff inflation. Diameter was determined using an automated edge-detection algorithm, and blood flow was measured from the velocity-time integral of the Doppler signal. FMD was defined as the maximal percentage change in vessel diameter after reactive hyperemia.

Plasma samples were used to measure PUA on the Architect c8000 Clinical Chemistry System using the manufacturer's reagents (Abbott Diagnostics, Abbott Park, IL).

Statistical Analysis

Continuous data are presented as mean \pm SD. For assessment of between-group differences, ANCOVA was used. Pearson correlation analyses were used to assess the relationship between renal parameters, urinary/plasma markers, and PUA levels. Regression analysis was used to assess the impact of covariates on continuous outcomes. Based on known factors that influence PUA levels, potentially relevant clinical characteristics that were included as the covariates in regression analysis were systolic blood pressure (SBP), sex,

HbA_{1c}, BMI, age, T1D duration, and plasma HDL cholesterol. *P* < 0.01 was considered statistically significant to account for multiple comparisons. All statistical analyses were performed using SAS, version 9.1.3, and GraphPad Prism software (version 5.0).

RESULTS

Baseline Demographic Characteristics and PUA Levels

The adolescent participants were normotensive and normoalbuminuric. Baseline parameters, such as sex distribution, age, blood pressure, eGFR, and ACR were similar between HC and T1D adolescents (Table 1). T1D patients had a higher BMI compared with HC. Of the 188 T1D patients, 133 exhibited normofiltration (71%) and 55 hyperfiltration (29%). HbA_{1c}, plasma glucose, and plasma HDL cholesterol were higher in T1D compared with HC subjects. PUA was lower in T1D adolescents than in HC (Fig. 1) (242 ± 55 vs. 306 ± 74 μmol/L, *P* < 0.0001). In the T1D cohort, insulin doses did not correlate with PUA levels and also did not

correlate with clinical parameters including SBP, eGFR, and log ACR.

No significant differences were observed in PUA levels between tertiles of spot check blood glucose levels or tertiles of HbA_{1c} in our T1D adolescent cohort (Supplementary Fig. 1A and B).

Association Between PUA and Renal Function

Higher PUA correlated with lower eGFR in the HC and T1D cohorts (Fig. 2) (*r* = −0.41, *P* = 0.0007, for HC and *r* = −0.48 and *P* < 0.0001 in T1D). With use of the Fisher z transformation technique, these correlations did not differ between the two cohorts (*P* = 0.4). Within patients with T1D, PUA levels were significantly higher in subjects with normofiltration compared with those with hyperfiltration (Supplementary Fig. 1C) (*P* < 0.0001). The association between PUA and eGFR remained significant after correction for SBP z score, sex, HbA_{1c}, BMI z score, age, T1D duration, and blood HDL cholesterol in the regression analysis of patients with T1D

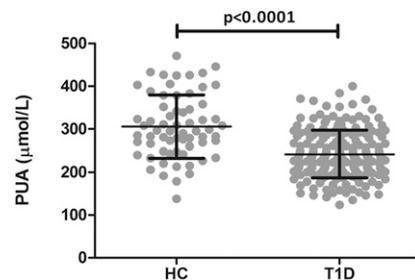


Figure 1—PUA levels in HC subjects (*n* = 65) and patients with T1D (*n* = 188). Data are presented as mean ± SD.

(β = −0.78, *P* < 0.0001). This observation was also present in T1D adolescents when patients with hyperfiltration were removed from the analysis (β = −1.08, *P* = 0.003). In contrast, in HC, after we controlled for SBP z score, sex, HbA_{1c}, BMI z score, age, and blood HDL cholesterol, the association between PUA and eGFR was not significant (β = −0.39, *P* > 0.01). These relationships remained the same when plasma glucose rather than HbA_{1c} was used in the regression model.

In the T1D cohort, higher PUA levels correlated with lower ACR (*r* = −0.20, *P* = 0.005, using log-transformed ACR), an association that was no longer significant after adjustment for eGFR, sex, HbA_{1c}, BMI z score, age, T1D duration, and blood HDL cholesterol and correction for multiple comparisons (β = −25.0, *P* > 0.01). When plasma glucose rather than HbA_{1c} was used in the model, the association did not change and was still not significant (β = −20.4, *P* > 0.01). The association between PUA and log ACR in HC participants was not observed (*r* = −0.17, *P* > 0.01). PUA levels were lower in each of the ACR tertile groups compared with HC. There were no differences in PUA levels observed between the three T1D ACR tertile groups studied in the cohort (Supplementary Fig. 1D).

Association Between PUA and Vascular Function

PUA did not correlate with SBP z score in HC (Supplementary Fig. 2) (*r* = −0.06, *P* > 0.01) or T1D (*r* = 0.04, *P* > 0.01). As shown in Supplementary Fig. 2, there was also no association observed after correction for clinical covariates in HC (β = 1.7, *P* > 0.01) or T1D (β = 3.8, *P* > 0.01). PUA did not correlate with PWV, diastolic

Table 1—HC and T1D subject characteristics at baseline

Parameter	HC (<i>n</i> = 65)	T1D (<i>n</i> = 188)
Baseline demographic parameters		
Male sex, <i>n</i> (%)	28 (43)	93 (49)
Age (years)	14.0 ± 2.0	14.4 ± 1.7
Diabetes duration (years)		7.2 ± 3.2
BMI (z score)	0.11 ± 1.15	0.65 ± 0.91
Baseline biochemistry		
HbA _{1c} , % (mmol/mol)	5.4 ± 0.2 (35.3 ± 2.7)	8.5 ± 1.3 (69.3 ± 13.8)*
PUA (μmol/L)	306 ± 74	242 ± 55*
Plasma glucose	4.7 ± 0.7	9.7 ± 4.3*
Total cholesterol	4.2 ± 0.8	4.3 ± 0.9
HDL cholesterol	1.5 ± 0.3	1.6 ± 0.4*
LDL cholesterol	2.4 ± 0.7	2.3 ± 0.7
Triglyceride	0.9 ± 0.4	0.8 ± 0.4
Renal function assessments		
eGFR (mL/min)	121 ± 22	127 ± 29
ACR	1.1 ± 1.6	1.0 ± 1.5
Vascular function assessments		
HR (bpm)	67 ± 10	67 ± 8
SBP (mmHg)	111 ± 8	113 ± 9
DBP (mmHg)	62 ± 7	63 ± 6
SBP (z score)	0.06 ± 0.72	0.19 ± 0.80
DBP (z score)	−0.18 ± 0.58	−0.16 ± 0.61
FMD (%)	7.6 ± 3.3	6.5 ± 3.1
Carotid femoral PWV (m/s)	5.2 ± 0.8	5.2 ± 0.7
Insulin therapy		
Insulin pump users, <i>n</i> (%)		116 (62)
Insulin injection users, <i>n</i> (%)		72 (38)
Insulin dose (units/kg)		1.00 ± 0.29

Data are means ± SD. HR, heart rate. **P* < 0.05 vs. HC.

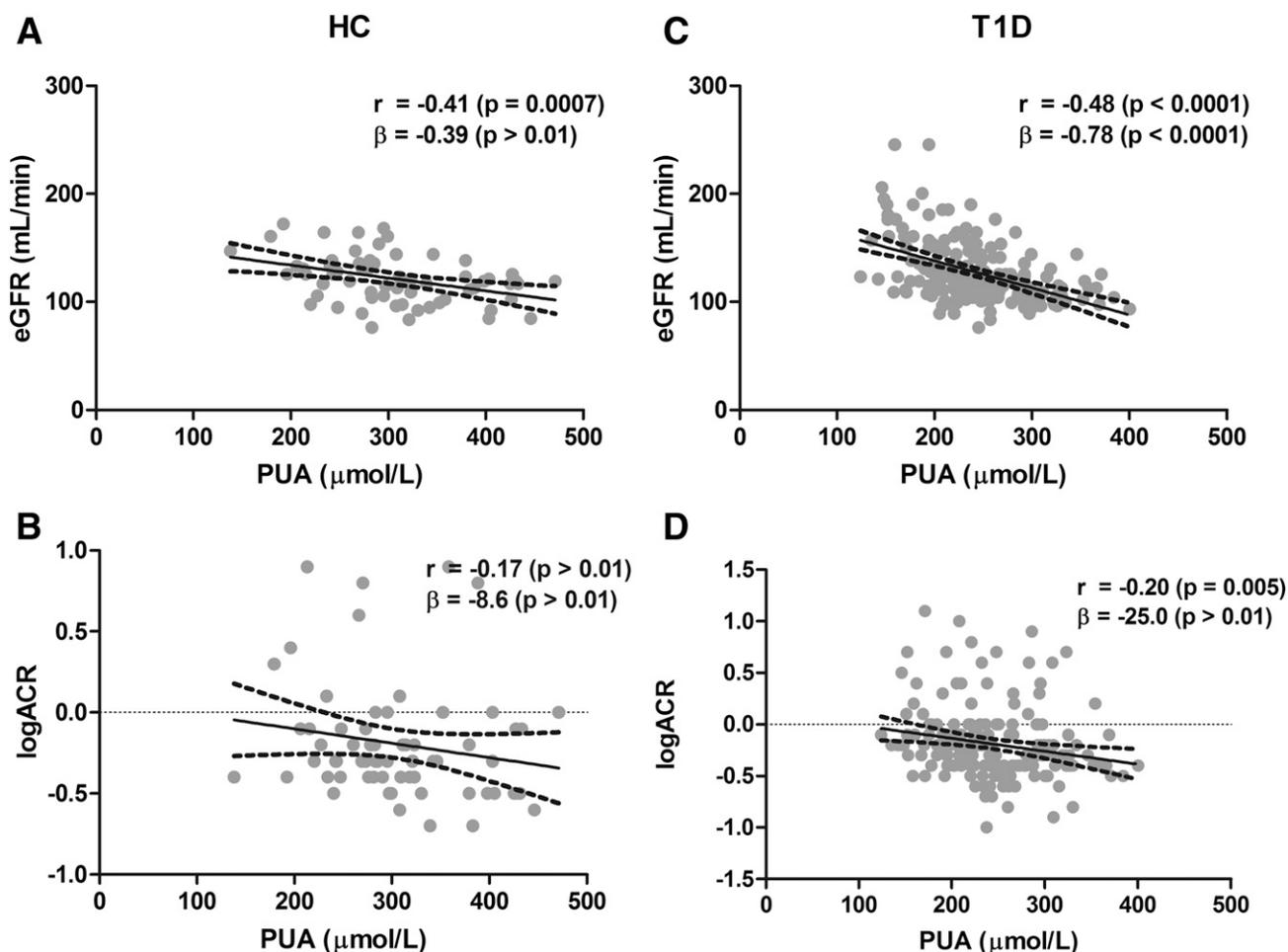


Figure 2—The relationship between eGFR, log transformation of ACR, and PUA in HC subjects (A and B) ($n = 65$) and patients with T1D (C and D) ($n = 188$). Pearson correlation analysis was used to obtain r and its associated P value. The β -coefficient with the associated P value was obtained from the regression analysis. In the HC PUA and eGFR regression analysis, the covariates were SBP z score, sex, HbA_{1c}, BMI z score, age, and plasma HDL cholesterol. In the T1D PUA and eGFR regression analysis, the covariates were SBP z score, sex, HbA_{1c}, BMI z score, age, diabetes duration, and plasma HDL cholesterol. In the HC PUA and log ACR regression analysis, the covariates were eGFR, sex, HbA_{1c}, BMI z score, age, and plasma HDL cholesterol. In the T1D PUA and log ACR regression analysis, the covariates were eGFR, sex, HbA_{1c}, BMI z score, age, diabetes duration, and plasma HDL cholesterol.

blood pressure (DBP) z score, or FMD in either group (Supplementary Fig. 2).

CONCLUSIONS

Although T1D complications are rarely evident during childhood, pathogenic processes leading to end organ injury begin soon after diagnosis and may accelerate during puberty (18,19). It is therefore important to study potential preclinical mechanisms leading to early disease pathogenesis to facilitate the identification of high-risk patients and thereby implement early therapeutic prevention strategies. PUA levels are consistently associated with renal and cardiovascular complications in adults with T1D and predict incident albuminuria, rapid eGFR decline, diabetic retinopathy, and coronary artery calcification

(20,21). The influence of PUA levels on renal and cardiovascular function has not yet been carefully characterized in adolescent patients with uncomplicated T1D prior to the onset of clinical complications.

In the current cohort, significantly higher PUA levels were observed in adolescent HC compared with T1D, which is consistent with previous observations in young adults and in adolescents (7,8,22). Increased urinary glucose excretion is thought to be the key mechanism responsible for PUA lowering in patients with diabetes due to a stimulatory effect of urinary glucose on the GLUT9 isoform 2 transporter on the apical membrane of the proximal tubule, which increases UA excretion in in vitro studies (23). Importantly, we have

previously demonstrated that impairing proximal tubule glucose reabsorption increases fractional excretion of uric acid in adults with T1D (7). Interestingly, and in contrast with our previous observations in young adults with T1D, neither HbA_{1c} nor plasma glucose levels significantly influenced PUA in our T1D adolescent cohort. It is thus possible that glycosuria does not modify PUA excretion in adolescents with T1D by the same mechanisms as in adults and that a longer T1D duration is required for higher glucose levels to influence PUA. It will therefore be important to confirm our observation in a larger cohort of adolescents over a longer period of time.

Previous longitudinal studies have shown a relationship between PUA and renal function decline. For example,

the second Joslin Study on the Natural History of Microalbuminuria showed a significant correlation between baseline PUA levels and early eGFR loss over a 6-year time period in older patients with T1D (24). Even in normoalbuminuric patients with T1D, Krolewski et al. (25) reported that mildly elevated PUA is an independent predictor of early eGFR loss. We also recently showed that higher PUA levels within the normal range are associated with lower GFR and effective renal plasma flow and higher renal vascular resistance in an adult T1D cohort without any complications (7,8). Consistent with the previous body of work in adults, the association between higher PUA and lower eGFR was present in our even earlier adolescent cohort of otherwise healthy T1D patients. This association persisted even after correction for SBP z score, sex, HbA_{1c}, BMI z score, age, T1D duration, and blood HDL cholesterol. Although we were not able to elucidate the mechanisms, this association is most likely on the basis of increased renal clearance, leading to lower PUA levels. However, the persistent association between higher PUA and lower eGFR in T1D adolescents with normofiltration suggests that hyperfiltration might not be the only factor driving this association. Thus, higher PUA may be linked with lower eGFR through renal vasoconstriction resulting in ischemia (8,26), but this seems unlikely in a pediatric cohort.

Microalbuminuria is a risk factor for progressive renal function decline (27) and is one of the first clinical markers of nephropathy in adolescents with T1D (11,28). Post hoc analyses of the Coronary Artery Calcification in Type 1 Diabetes study (CACTI) reported that over a 6-year follow-up period, each 60 $\mu\text{mol/L}$ increase in PUA from baseline elevated the risk of micro- or macroalbuminuria by 80% in 652 normoalbuminuric patients (29). Similarly, Hovind et al. (30) reported that baseline PUA levels predict the development of macroalbuminuria over 18 years of follow-up in patients with T1D. In our cohort, in the univariate analysis, higher PUA was modestly associated with lower ACR. However, this interaction was no longer significant after adjustment for clinical characteristics, suggesting the predominant role of other pathways,

including the interaction between PUA and eGFR, that mediate changes in albumin excretion. Furthermore, there was no difference in baseline PUA levels in the low, middle, and high risk within normal-range ACR tertiles in the T1D adolescent patients. Overall, our data suggest that baseline PUA levels in this cohort are not associated with ACR at this early stage of T1D.

Accumulating evidence in patients with hypertension, atherosclerosis, and type 2 diabetes, and also in HC subjects, suggests that increased PUA levels, even within the normal range, may be associated with endothelial dysfunction and vascular stiffness (1), thereby promoting cardiovascular disease. A National Health and Nutrition Examination Survey (1999–2006) found that PUA of $>327 \mu\text{mol/L}$ in 6,036 adolescents carried a twofold risk of developing hypertension (31). We also recently reported an association between higher PUA and higher blood pressure within the normal range in young adults with uncomplicated T1D (7,32). In our cohort of adolescents with uncomplicated T1D or in HC subjects, PUA did not correlate with SBP z score, PWV, or FMD (a measure of endothelial function) after correction for age, sex, HbA_{1c}, BMI z score, T1D duration, and HDL. It is therefore possible that the relationship between PUA and blood pressure could be altered over time according to duration of the disease or age in patients with T1D (7).

Our study has limitations. The patient study cohort consisted of a carefully selected group with no complications in a subset of patients from AddIT. Thus, our data may only be relevant to adolescent patients with uncomplicated T1D and cannot necessarily be extended to other conditions. Data on urinary glucose levels were not available, and thus the association between PUA and glycosuria could not be studied. Dietary consumption of UA-rich foods, such as purine-containing products, was also not recorded and thus could not be taken into account in the analysis. We also recognize that this analysis included a subset of participants in the AddIT observation cohort. As such, our observations should be considered exploratory in nature and ultimately require confirmation using a larger sample size of patients. Finally,

future analyses should examine whether PUA levels are influenced by puberty stage—an interaction that was not examined in this cohort.

In conclusion, even within the physiological range, PUA levels were significantly lower in T1D adolescent patients compared with HC subjects. There was an inverse relationship between PUA and eGFR in T1D, and no associations were observed with blood pressure, arterial stiffness, or endothelial function. Thus, in contrast with adults, in adolescents with T1D PUA may not yet be associated with cardio-renal abnormalities, highlighting the need to determine whether the effect of PUA on renal risk is modified over time.

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