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Serum uric acid and insulin sensitivity in adolescents and adults with and without type 1 diabetes

Petter Bjornstad, M.D.¹, Janet K. Snell-Bergeon, Ph.D., M.P.H.^{1,2}, Kimberly McFann, Ph.D.³, R. Paul Wadwa, M.D.^{1,2}, Marian Rewers, M.D., Ph.D.^{1,2}, Christopher J. Rivard, Ph.D.⁴, Diana Jalal, M.D.³, Michel B. Chonchol, M.D.⁴, Richard J. Johnson, M.D.⁴, and David M. Maahs, M.D., Ph.D.^{1,2,4}

¹Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

²Barbara Davis Center for Diabetes, University of Colorado Denver, Aurora, CO

³University of Colorado School of Public Health, Colorado Biostatistics Consortium, Aurora, CO

⁴Department of Nephrology, University of Colorado Denver, Aurora, CO

Abstract

Hypothesis—Decreased insulin sensitivity (IS) exists in type 1 diabetes. Serum uric acid (SUA), whose concentration is related to renal clearance, predicts vascular complications in type 1 diabetes. SUA is also inversely associated with IS in non-diabetics, but has not been examined in type 1 diabetes. We hypothesized SUA would be associated with reduced IS in adolescents and adults with type 1 diabetes.

Methods—The cross-sectional and longitudinal associations of SUA with IS was investigated in 254 adolescents with type 1 diabetes and 70 without in the Determinants of Macrovascular Disease in Adolescents with Type 1 Diabetes Study, and in 471 adults with type 1 diabetes and 571 without in the Coronary Artery Calcification in Type 1 diabetes (CACTI) study.

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Address all correspondence to: Petter Bjornstad, M.D., Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, 1775 Aurora Court, Aurora, CO 80045, Phone: 720.579.1048, Fax: 303.724.6779, Petter.Bjornstad@childrenscolorado.org.

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Author Contributions

PB researched, wrote, contributed to discussion, and reviewed/edited the manuscript; JKSB researched, contributed to the discussion, reviewed/edited the manuscript; MR designed the CACTI Study, researched, contributed to the discussion and reviewed/edited the manuscript; KM formulated the analytic plan, performed the statistical analyses and reviewed/edited the manuscript; RPW designed the Determinants of Macrovascular Disease in Adolescents with Type 1 Diabetes Study, researched, contributed to the discussion and reviewed/edited the manuscript; DJ contributed to the discussion and reviewed/edited the manuscript; CJR was responsible for the laboratory analyses, contributed to the discussion and reviewed/edited the manuscript; MC contributed to the discussion and reviewed/edited the manuscript; RJJ contributed to the discussion and reviewed/edited the manuscript; DMM researched, contributed to discussion, and reviewed/edited the manuscript.

Duality of interest

RJJ has patent applications related to the lowering of uric acid and or blocking fructose metabolism as a means for slowing diabetic nephropathy or improving insulin resistance, and has shares with XORT Therapeutics related to these patents. Drs. Bjornstad, Snell-Bergeon, McFann, Wadwa, Rewers, Rivard, Jalal, Chonchol and Maahs have no conflict of interest to disclose.

Results—SUA was lower in subjects with type 1 diabetes ($p<0.0001$), but still remained inversely associated with IS after multivariable adjustments- in adolescents ($\beta\pm\text{SE}$: -1.99 ± 0.62 , $p=0.001$, $R^2=2\%$) and adults ($\beta\pm\text{SE}$: -0.91 ± 0.33 , $p=0.006$, $R^2=6\%$) with type 1 diabetes, though less strongly than in non-diabetic controls (adolescents: $\beta\pm\text{SE}$: -2.70 ± 1.19 , $p=0.03$, $R^2=15\%$, adults: $\beta\pm\text{SE}$: -5.99 ± 0.75 , $p<0.0001$, $R^2=39\%$).

Conclusion—We demonstrated a significantly weaker relationship between SUA and reduced IS in subjects with type 1 diabetes than non-diabetic controls.

Keywords

insulin sensitivity; type 1 diabetes; serum uric acid; adolescents and adults

Introduction

Reduced insulin sensitivity is well documented in both adolescents and adults with type 1 diabetes, and is thought to contribute both to the initiation and progression of macro- and microvascular complications (1, 2). The exact mechanism of reduced insulin sensitivity in type 1 diabetes is poorly understood, but is not completely explained by body mass index (BMI), visceral fat, physical activity, hyperglycemia or systemic inflammation (3, 4). Significantly higher prevalence of metabolic syndrome (38% in men and 40% in women) has also been reported in subjects with type 1 diabetes than non-diabetic subjects (5), although the definition of metabolic syndrome in type 1 diabetes may not be directly comparable to non-diabetic subjects. Several factors have been implicated including prolonged exposure to supraphysiologic levels of exogenous insulin, loss of the insulin sensitizing effect of plasma palmitoleic acid and the genetic and environmental factors that lead to type 2 diabetes (4, 6–9).

Hyperuricemia was historically viewed as a consequence of the effects of insulin to increase renal uric acid reabsorption (10). However, more recent studies have reported that SUA can also predict the development of hyperinsulinemia, metabolic syndrome and type 2 diabetes (11–14) likely via its intracellular effects on the liver, adipocyte and endothelial cell. Subjects with type 1 diabetes have reduced SUA concentrations (15, 16), but there is still robust evidence linking SUA to vascular complications in type 1 diabetes (17–19). SUA and insulin sensitivity remain attractive therapeutic targets due to the availability of generic medications like allopurinol and metformin. Little, if any data, however, exist on a possible association between SUA and insulin sensitivity in type 1 diabetes, and whether they are independent pathways in vascular pathogenesis, or as strongly associated as what is observed in subjects without type 1 diabetes. For that reason, further data are needed on the relationship between SUA and insulin sensitivity in type 1 diabetes.

SUA levels tend to increase with age, and the relationship between SUA and insulin sensitivity might change over time as patients become older. Accordingly, we explored the association between SUA and insulin sensitivity among adolescent and adults with type 1 diabetes. We hypothesized that SUA would be associated with insulin sensitivity cross-sectionally, and that baseline SUA would predict worsening of insulin sensitivity over 2 and 6 years respectively in adolescents and adults with and without type 1 diabetes.

Materials and Methods

The Determinants of Macrovascular Disease in Adolescents with type 1 diabetes study cohort

The Determinants of Macrovascular Disease in Adolescents was initiated to investigate atherosclerotic disease risk in youth with and without type 1 diabetes. The study enrolled subjects 12–19 years old, with and without type 1 diabetes. Study participants with type 1 diabetes were diagnosed by islet cell antibody or by provider clinical diagnosis, had diabetes duration >5 years at entry into the study, and received care at the Barbara Davis Center for Childhood Diabetes, Aurora, Colorado. Control subjects were recruited from friends of the study subjects as well as from campus and community advertisements. No siblings or first-degree relatives of patients with type 1 diabetes were included. Subjects were excluded for diabetes of any other type and for any history of abnormal cardiac anatomy or arrhythmia that would preclude the subject from vascular function measurements. All subjects with data available for SUA and estimated insulin sensitivity (eIS) were included in this analysis, which included 254 adolescents with type 1 diabetes and 70 controls at baseline and 193 adolescents with type 1 diabetes and 50 controls at 2-year follow-up. The study was approved by the Colorado Multiple Institution Review Board, and informed consent and assent (for subjects <18 years) was obtained from all subjects.

After subjects had been laying supine for a minimum of 5 minutes, blood pressure measurements were obtained using a Dynapulse 5200A (Pulse Metric, San Diego, California), and 3 measurements were averaged. Height was measured to the nearest 0.1 cm with shoes removed using a wall-mounted stadiometer, and weight was measured to the nearest 0.1 kg using a Detecto scale (Detecto, Webb City, Missouri). Waist circumference was measured at the navel on bare skin using the Figure Finder Tape Measure by Novel Products (Rockton, Illinois), which provides consistent and repeatable oz of tension and accuracy to 3/32 inch.

All subjects fasted overnight (8 hours). HbA1c was measured on the DCA Advantage by Siemens (Princeton, New Jersey). Total cholesterol, high-density lipoprotein cholesterol (HDL-c), and triglycerides were performed using an Olympus AU400e Chemistry (Olympus, Brea, California). Low-density lipoprotein cholesterol was calculated using the Friedwald formula. High-sensitivity C-reactive protein was measured using a multiplex assay platform Siemens (formally Dade Behring) BNII Nephelometer. Serum creatinine was measured using an Olympus AU400e, and urinary creatinine was measured by the Jaffe method using Roche Diagnostics reagent on the Hitachi 917 autoanalyzer. Serum uric acid levels were measured on stored baseline samples via the Clinical Analyzer utilizing a uricase-based commercial kit. Urinary uric acid was analyzed without dilution for uric acid using the ACE autoanalyzer (Alfa Wassermann, West Caldwell, NJ) employing the uricase method with final endpoint analysis. Fractional excretion of uric acid calculated by: $FeUA = [(urinary\ uric\ acid) * (serum\ creatinine) * (100\%)] / [(serum\ uric\ acid) * (urinary\ creatinine)]$. All uric acid measures were performed in the laboratory of Dr. Richard Johnson.

Insulin sensitivity for adolescents was calculated by Insulin Sensitivity Score (eIS) model derived from SEARCH Clamp Study: $\log eIS = 4.64725 - 0.02032 (\text{waist [cm]}) - 0.09779 (\text{HbA1c [\%]}) - 0.00235 (\text{TG [mg/dL]})$ ($R^2 = 0.74$ in the initial SEARCH model) (20).

The Coronary Artery Calcification in Type 1 diabetes (CACTI) Cohort

The CACTI Study enrolled subjects 19–56 years old, with and without type 1 diabetes, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–02 and then were re-examined 3 and 6 years later, as previously described (21). Subjects with serum creatinine $>2\text{mg/dl}$ were excluded at baseline, unless they were participants in the pilot study. Data on baseline SUA and insulin sensitivity at baseline were available for 471 patients with type 1 diabetes and 571 controls, and follow-up SUA and insulin sensitivity at 6 years were available for 420 patients with type 1 diabetes and 513 controls. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

We measured height and weight, and calculated body mass index (BMI) in kg/m^2 . Resting systolic (SBP) and fifth-phase diastolic blood pressure (DBP) were measured three times while the patient was seated, and the second and third measurements were averaged. Hypertension was defined as current anti-hypertensive therapy or untreated hypertension (BP 140/90 mmHg) at the time of the study visit. Anti-hypertension medication use was determined by a medication inventory as previously described (21) and use of an ACE inhibitor (ACEi) or an angiotensin receptor blocker (ARB) were combined for these analyses.

Serum uric acid levels were measured on stored baseline samples via the Clinical Analyzer utilizing a uricase-based commercial kit. These samples had been thawed twice in the past. The results were reported in milligrams per deciliter. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods, HDL cholesterol was separated using dextran sulfate and LDL cholesterol was calculated using the Friedewald formula. High performance liquid chromatography was used to measure HbA1c (HPLC, BioRad variant). Serum creatinine was measured according to package insert instructions using a Roche Mira Plus II analyzer until 2006 and then an Olympus AU400e ($r=0.9999$ between methodologies) traceable to the National Institutes of Standards and Technology Standard Reference Material in the University of Colorado Clinical Translational Research (CTRC) Lab and standardized longitudinally as previously described (22).

Two timed overnight urine samples were collected in duplicate and urine creatinine and albumin were measured (RIA, Diagnostic Products) and averaged. Insulin sensitivity was calculated by Insulin Sensitivity Index (ISI) model derived from CACTI clamp studies (23). The equation to calculate ISI explained 63% of the variance in the glucose disposal rate (GDR). The equation to calculate the ISI is: $\exp(4.1075 - 0.01299 \cdot \text{waist (cm)} - 1.05819 \cdot \text{insulin dose (daily units per kg)} - 0.00354 \cdot \text{triglycerides (mg/dl)} - 0.00802 \cdot \text{diastolic blood pressure (mm Hg)})$ (24).

Statistical Analysis

Analyses were performed in SAS (version 9.3 for Windows; SAS Institute, Cary, NC). Differences between type 1 diabetes patients and normal controls were assessed using Chi-Square for categorical variables and t-test for continuous variables. Variables with skewed distributions (e.g. SUA and serum creatinine) were log-transformed and then back transformed to compute geometric means. Linear regression and ANCOVA were employed to fit three models with baseline LnSUA as a continuous predictor and then quartiles of SUA as categorical predictors of baseline insulin sensitivity and change in insulin sensitivity: unadjusted model, model 1 adjusted for age, sex, BMI and LnSCr, model 2 adjusted for model 1 + disease duration, SBP, HbA1c, LDL-c, HDL-c, fasting blood glucose and current smoking status. In the adolescent cohort, we further adjusted for FeUA in an attempt to control for the proposed uricosuric effect observed in subjects with type 1 diabetes.

In adolescent and adult cohorts, we had 2 and 6-year follow-up data, respectively, to explore longitudinal relationships. We defined worsening of insulin sensitivity as a decrease from baseline insulin sensitivity over time. Logistic regression was used to see if baseline SUA predicted worsening of insulin sensitivity in type 1 diabetes and controls. For linear regression, data are presented as $\beta \pm \text{SE}$. For ANCOVA, data are presented as least square mean $\pm \text{SE}$. For logistic regression, data are presented as OR (95% CI). All analyses were stratified by type 1 diabetes status, and significance was based on an α -level of 0.05.

Results

The Determinants of Macrovascular Disease in Adolescents with type 1 diabetes study

Type 1 diabetes patients had higher HbA1c, higher SBP, slightly lower serum creatinine, lower SUA, lower insulin sensitivity, and higher LDL compared to controls (Table 1). FeUA did not differ by diabetes status ($p=0.91$, Table 1) and, as expected, was negatively correlated with Ln SUA ($r=-0.23$, $p<0.0001$).

Cross-sectionally in type 1 diabetes, Ln SUA was negatively correlated with insulin sensitivity in unadjusted analyses ($\beta \pm \text{SE}$: -1.93 ± 0.82 , $p=0.02$), and explained only 2% of the variability of insulin sensitivity. In comparison, BMI accounted for 28% and HbA1c 37% of the variability of insulin sensitivity respectively. After adjustments for FeUA, age, sex, BMI, serum creatinine, type 1 diabetes duration, SBP, HbA1c, HDL, LDL, and current smoking, Ln SUA remained negatively associated with eIS ($\beta \pm \text{SE}$: -1.99 ± 0.62 , $p=0.001$, Table 2). Moreover, in the same multivariable-adjusted model the 4th quartile of SUA was associated with lower eIS than the 1st quartile of SUA ($p=0.04$, Table 2).

Cross-sectionally in controls, Ln SUA was negatively correlated with insulin sensitivity in unadjusted analyses ($\beta \pm \text{SE}$: -5.80 ± 1.70 , $p=0.001$) and explained 15% of the variability in insulin sensitivity (Figure 1A). In comparison, HbA1c accounted for 4% and BMI 72% of the variability of insulin sensitivity, respectively. After multivariable adjustments the association between Ln SUA and eIS remained significant ($\beta \pm \text{SE}$: -2.70 ± 1.19 , $p=0.03$, Table 3). There was also an association between quartiles of SUA and eIS ($p=0.048$) (Table 2).

Longitudinally, SUA at baseline was not associated with increased odds of worsening of eIS over 2 years in subjects with type 1 diabetes (OR = 0.14, 95% CI: 0.01–1.69, $p=0.12$) or controls (OR = >999, 95% CI: 0.28–>999, $p=0.08$).

The Coronary Artery Calcification in Type 1 diabetes (CACTI) Cohort (Adults)

There were several differences between those with type 1 diabetes and controls; type 1 diabetes patients were younger, had higher HbA1c, lower SUA at baseline and 6 years, lower insulin sensitivity at baseline and 6 years, higher HDL-c and lower LDL-c (Table 2).

Cross-sectionally in type 1 diabetes, Ln SUA was negatively correlated with ISI in unadjusted analyses ($\beta \pm \text{SE}$: -1.90 ± 0.34 , $p < 0.0001$) and explained only 6% of the variability of ISI (Figure 1B). In comparison, HbA1c accounted for 8% and BMI for 28% of the variability of ISI, respectively. After adjustments for age, sex, BMI, serum creatinine, type 1 diabetes duration, SBP, HbA1c, HDL, LDL, and current smoking, Ln SUA remained negatively associated with ISI ($\beta \pm \text{SE}$: -0.91 ± 0.33 , $p=0.006$, Table 4). Moreover, in a fully adjusted model the 4th quartile was associated with lower insulin sensitivity than the 1st quartile of SUA ($p=0.04$) (Table 4).

Cross-sectionally in controls, Ln SUA was negatively correlated with ISI in unadjusted analyses ($\beta \pm \text{SE}$: -18.19 ± 0.96 , $p < 0.0001$), and explained 39% of the variability of ISI (Figure 1B). In comparison, HbA1c accounted for 33% and BMI 41% of the variability of ISI, respectively. After multivariable adjustments, Ln SUA remained negatively associated with ISI ($\beta \pm \text{SE}$: -5.99 ± 0.75 , $p < 0.0001$, Table 4). The 4th quartile of SUA was also associated with lower ISI than the 1st, 2nd and 3rd quartiles. In a fully adjusted model the 4th quartile was still significantly associated with lower ISI than the 1st, 2nd and 3rd quartiles of SUA ($p < 0.0001$) (Table 4).

Longitudinally, a one mg/dL increase in SUA from baseline to 6 years was associated with increased odds of worsening ISI in controls (OR = 1.59, 95% CI: 1.30–1.93, $p < 0.0001$), while an increase in SUA was not associated with worse ISI in type 1 diabetes (OR = 1.05, 95% CI: 0.86–1.27, $p = 0.65$).

Conclusions

SUA and insulin sensitivity are both implicated in vascular complications in type 1 diabetes. The association between SUA and reduced insulin sensitivity is well-recognized in type 2 diabetes and metabolic syndrome, but has not previously been investigated in type 1 diabetes. In this study, we report lower levels of SUA in adolescents and adults with type 1 diabetes, and a weak inverse relationship between SUA and insulin sensitivity in both adolescents and adult subjects with type 1 diabetes. In contrast, in non-diabetic adolescents and adults SUA accounted for a significantly greater amount of the variability of insulin sensitivity, and a longitudinal association was also observed between SUA and worsening insulin sensitivity in adult subjects. These data suggest that even though subjects with type 1 diabetes have lower insulin sensitivity than their non-diabetic counterparts, the association observed between SUA and reduced insulin sensitivity in non-diabetic subjects is less strong in those with type 1 diabetes. Furthermore, the associations between SUA and reduced

insulin sensitivity were stronger among adults than adolescent subjects with and without type 1 diabetes, suggesting the relationship between SUA and insulin sensitivity may strengthen over time as patients become older. Few, if any, studies have examined the association between SUA and reduced insulin sensitivity across a wide age span (12–56 years) in subjects with and without type 1 diabetes, which is a strength of our study.

The exact mechanism linking SUA and reduced insulin sensitivity in non-diabetic subjects remains unclear. Elevated levels of SUA have been observed with reduced insulin sensitivity and were historically attributed to hyperinsulinemia, as insulin reduces renal excretion of SUA (10). However, increased SUA often precedes the development of hyperinsulinemia. The strongest evidence of a role for SUA in the development of worsening insulin sensitivity comes from studies in animal models showing that decreasing SUA may prevent or even reverse features of reduced insulin sensitivity (25, 26). A number of mechanisms have been suggested by which SUA could affect insulin sensitivity. Elevated SUA has been found to be associated with oxidative stress, systemic inflammation and endothelial dysfunction induced by decreased endothelial nitric oxide production, all of which play roles in the development of impaired insulin sensitivity (27, 28). There is also supporting evidence that fructose-induced elevation of SUA may have a pathogenic role in reduced insulin sensitivity (29, 30). Nakagawa et al. showed that in rats receiving a high-fructose diet, the lowering of SUA with either allopurinol or benzobromarone prevented features of metabolic syndrome and insulin resistance (29). There is to our knowledge, however, no mechanistic data exploring the association between SUA and insulin sensitivity in type 1 diabetes.

The reduced concentrations of SUA observed in subjects with type 1 diabetes, as well as the weaker association between SUA and insulin sensitivity may be due to the effect of intermittent glycosuria that occurs in diabetes. SUA levels have been shown to fall in subjects once they become diabetic, as glycosuria may lead to proximal tubular dysfunction and uricosuria (31). For that reason SUA may actually decrease in people with diabetes, especially if they are poorly controlled. We included measurements of concurrent fasting blood glucose and HbA1c in both cohorts and FeUA in the adolescent cohort in an attempt to control for the potential effect of hyperglycemia on urinary excretion of uric acid. Adjusting for these variables did not change the relationships between SUA and insulin sensitivity in our cohorts. Furthermore, FeUA was the same in adolescents subjects with and without T1D (4.6 vs. 4.6, $p=0.9$), despite significantly different HbA1c (9.0 vs. 5.3, $p<0.0001$). For these reasons the uricosuric effect is unlikely to explain the differences observed in adolescents with type 1 diabetes and normal controls. We were unable to test this hypothesis in the adult cohort. Another possible explanation for the weaker association observed between SUA and reduced insulin sensitivity in subjects with type 1 diabetes is that the phenotype of reduced insulin sensitivity in type 1 diabetes might differ from that of type 2 diabetes/metabolic syndrome. The hypothesis of different phenotypes is supported by the observation of insulin resistance in type 1 diabetes, despite elevated levels of adiponectin, an adipocyte-secreted protein important in determination of insulin sensitivity (32), which stands in contrast to type 2 diabetes where there is a well-recognized inverse relationship between adiponectin and insulin resistance (33). Furthermore, insulin resistance

has been documented in type 1 diabetes subjects with normal BMI and HbA1c (34) and cannot be explained by plasma lipids, visceral fat or systemic inflammation (3, 4).

The weak association we report between SUA and reduced insulin sensitivity in adolescent and adult subjects with type 1 diabetes stands in contrast with previous cross-sectional studies that showed a close relation between SUA and reduced insulin sensitivity in adolescents and adults without type 1 diabetes (35–37).

Insulin sensitivity is recognized to play an important role in the development of vascular complications in type 1 diabetes (2, 38, 39), and SUA has been shown to predict both the development of albuminuria (40–42) and progression of coronary artery calcification (19) in subjects with type 1 diabetes. In non-diabetic subjects and subjects with type 2 diabetes, there is a strong association between SUA and reduced insulin sensitivity. For that reason one could hypothesize that insulin sensitivity and SUA are two components of the same pathway leading to vascular complications in type 1 diabetes. However, the evidence of a significantly weaker association between SUA and reduced insulin sensitivity in type 1 diabetes, suggests SUA and insulin sensitivity may represent separate pathways in type 1 diabetes, and offer promise for their role as independent therapeutic targets in the prevention of vascular complications. There are clinical trials under way to lower SUA and to improve insulin sensitivity in type 1 diabetes, including The Preventing Early Renal Function Loss (PERL) Allopurinol Study (17) and Reducing with Metformin Vascular Adverse Lesions in Type 1 Diabetes (REMOVAL) trial (43), respectively.

An important strength of our study is the large number of subjects with data available on important confounders across a wide age distribution. Unlike some previous studies, we did not limit our data to those with abnormally high levels of SUA and instead looked at SUA as a continuous variable and quartiles to explore the association with insulin sensitivity across the whole distribution of SUA. Our cohorts also offer important longitudinal data, which imply a causal relationship between SUA and insulin sensitivity in adults without type 1 diabetes.

The limitations of our study also deserve comment. The sample size of adolescent controls (n=50) with follow-up data was too small for any meaningful longitudinal multivariable analysis. The adolescent subjects with type 1 diabetes had higher BMI z-score than controls, but we adjusted for BMI in our multivariable models to account for this. Although we adjusted for a variety of important confounding variables, we cannot rule out the presence of unknown risk factors that may have biased or confounded the present analyses. Another important limitation is the lack of direct measures of insulin sensitivity due our large cohorts making hyperinsulinemic-euglycemic clamp studies too cumbersome; however both eIS and ISI have been validated in clamp studies and shown to explain 63% and 74% of the variability of insulin sensitivity in their respective cohorts. We only had FeUA data in our adolescent cohort, but adjusting for this variable neither changed the associations observed between SUA and insulin sensitivity, nor the difference observed between adolescent subjects with and without type 1 diabetes. It is uncertain whether adjusting for FeUA would have explained our observations in the adult cohort, but cannot be ruled out due to the significantly longer diabetes duration and renal involvement in our adult subjects. This is

also to our knowledge the first clinical study adjusting for this FeUA in an attempt to account for the uricosuric effect.

In conclusion, insulin sensitivity and levels of SUA were significantly lower in adolescents and adults with type 1 diabetes. In contrast to non-diabetic subjects, SUA only accounted for a small amount of the variability of insulin sensitivity in adolescents and adults with type 1 diabetes. There is compelling observational evidence linking both SUA and reduced insulin sensitivity respectively with vascular complications in type 1 diabetes. In this study we present evidence of a very weak association between SUA and reduced insulin sensitivity in type 1 diabetes, which is unlikely to be of clinical significance, and therefore stands in contrast to the strong association observed in non-diabetic subjects. The absence of a clinically significant association between SUA and reduced insulin sensitivity in type 1 diabetes is promising, and may suggest the independence of SUA and reduced insulin sensitivity as mediators of vascular pathogenesis in type 1 diabetes.

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Drs. David M Maahs, R. Paul Wadwa, Petter Bjornstad and Janet K. Snell-Bergeon are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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Figure 1.

Relationship of baseline LnUA with eIS in adolescent with and without type 1 diabetes
Relationship of baseline LnUA with ISI in adults with and without type 1 diabetes

Table 1

Characteristics of Adolescent Type 1 diabetes Patients and Controls

Variable	Means $\pm$ SD and p-values for comparisons by group		
	Type 1 diabetes (N = 254)	Controls (N = 70)	P-Value
Age (years)	15.4 $\pm$ 2.2	15.4 $\pm$ 2.2	0.85
Sex (Male)	49.6%	42.9%	0.32
Currently Smoking (%)	7.1%	7.1%	0.99
Duration (years)	8.7 $\pm$ 3.0	--	--
BMI Z-Score (kg/m ²)	0.6 $\pm$ 0.8	0.2 $\pm$ 1.1	0.002
HbA1c (%)	9.0 $\pm$ 1.6	5.3 $\pm$ 0.3	< 0.0001
HbA1c (mmol/mol)	75 $\pm$ 15	34 $\pm$ 1	< 0.0001
SCR (mg/dL)	0.65 $\pm$ 0.14	0.70 $\pm$ 0.15	0.01
SBP (mm Hg)	113 $\pm$ 8	108 $\pm$ 9	< 0.0001
Uric Acid (mg/dL)	4.6 $\pm$ 0.8	5.0 $\pm$ 1.0	< 0.0001
FeUA	4.6 $\pm$ 4.3	4.6 $\pm$ 4.3	0.91
eIS (mg/kg ⁻¹ min ⁻¹)	7.8 $\pm$ 2.4	11.7 $\pm$ 2.8	< 0.0001
HDL (mg/dL)	51 $\pm$ 10	49 $\pm$ 10	0.17
LDL (mg/dL)	89 $\pm$ 27	82 $\pm$ 22	0.03
Blood glucose (mg/dL)	183.4 $\pm$ 79.3	82.0 $\pm$ 7.2	<0.0001

Table 2
Relationship between baseline serum uric acid and insulin sensitivity in adolescents

Type 1 diabetes	Ln SUA	Quartile 1 of SUA	Quartile 2 of SUA	Quartile 3 of SUA	Quartile 4 of SUA
	$\beta^* \pm SE$ P-Value	Least square Mean $\pm SE$	Least square Mean $\pm SE$	Least square Mean $\pm SE$	Least square Mean $\pm SE$
eIS (unadjusted)	-1.93 $\pm$ 0.82 P = 0.02	8.52 $\pm$ 0.28**	7.75 $\pm$ 0.28	7.41 $\pm$ 0.35	7.16 $\pm$ 0.35
eIS (adjusted for FeUA)	-2.29 $\pm$ 0.89 P = 0.01	8.57 $\pm$ 0.29**	7.78 $\pm$ 0.30	7.48 $\pm$ 0.31	7.09 $\pm$ 0.36
eIS (adjusted for model 1: age, sex, BMI, LnSCr)	-2.50 $\pm$ 0.84 P = 0.003	8.33 $\pm$ 0.24**	7.66 $\pm$ 0.24	7.67 $\pm$ 0.25	7.35 $\pm$ 0.30
eIS (adjusted for model 2: model 1, SBP, diabetes duration, LDL-c, HDL-c, glucose and current smoking)	-1.99 $\pm$ 0.62 P = 0.001	8.26 $\pm$ 0.18**	7.73 $\pm$ 0.18	7.74 $\pm$ 0.19	7.42 $\pm$ 0.22
Controls	Ln SUA	Quartile 1 of SUA	Quartile 2 of SUA	Quartile 3 of SUA	Quartile 4 of SUA
	$\beta^* \pm SE$ P-Value	Least square Mean $\pm SE$	Least square Mean $\pm SE$	Least square Mean $\pm SE$	Least square Mean $\pm SE$
eIS (unadjusted)	-5.80 $\pm$ 1.70 P = 0.001	14.01 $\pm$ 0.88**	12.58 $\pm$ 0.64**	12.68 $\pm$ 0.64**	10.18 $\pm$ 0.44
eIS (adjusted for FeUA)	-5.70 $\pm$ 1.83 P = 0.003	13.92 $\pm$ 0.91**	12.73 $\pm$ 0.66**	12.47 $\pm$ 0.69**	10.23 $\pm$ 0.46
eIS (adjusted for model 1: age, sex, BMI, LnSCr)	-2.77 $\pm$ 1.09 P = 0.01	11.86 $\pm$ 0.51	12.34 $\pm$ 0.34**	11.84 $\pm$ 0.35	11.14 $\pm$ 0.24
eIS (adjusted for model 2: model 1, SBP, LDL-c, HDL-c, glucose, and current smoking)	-2.70 $\pm$ 1.19 P = 0.03	12.02 $\pm$ 0.54	12.40 $\pm$ 0.36	11.60 $\pm$ 0.37	11.24 $\pm$ 0.26

* β -coefficient represents the difference in estimated insulin sensitivity (eIS) for every 1-unit difference, and where appropriate for every natural log difference in the independent variable.

** P < 0.05 compared with the 4th Quartile.

Table 3

Characteristics of Adult Type 1 diabetes Patients and Controls

Variable	Visit 1		
	Type 1 diabetes (N = 471)	Controls (N = 571)	p-value
Age (years)	37 ± 9	40 ± 9	< 0.0001
Sex (Males)	47.1%	50.4%	--
NHW (%)	93%	80.7%	0.81
Duration (years)	23.0 ± 8.9	--	<0.0001
BMI (kg/m ²)	26.1 ± 4.2	26.0 ± 4.7	<0.0001
HbA1c (%)	7.9 ± 1.2	5.5 ± 0.4	0.95
HbA1c (mmol/mol)	63 ± 11	37 ± 2	0.02
SCR (mg/dL)	1.2 ± 0.2	1.2 ± 0.2	<0.0001
SBP (mmHg)	116 ± 13	114 ± 12	<0.0001
Uric Acid (mg/dL) baseline	5.0 ± 1.1	5.7 ± 1.3	0.04
Uric Acid (mg/dL) 6 Years	5.3 ± 1.2	6.1 ± 1.4	<0.0001
Change in Uric Acid (mg/dL)	0.3 ± 1.0	0.4 ± 1.0	<0.0001
ISI baseline (mg/kg ⁻¹ min ⁻¹)	4.4 ± 1.6	15.5 ± 6.6	<0.0001
ISI 6 Years (mg/kg ⁻¹ min ⁻¹)	4.7 ± 1.8	15.7 ± 6.6	<0.0001
HDL (mg/dL)	55 ± 16	51 ± 15	<0.0001
LDL (mg/dL)	99 ± 28	116 ± 34	<0.0001
Blood glucose (mg/dL)	184.1 ± 90.6	90.5 ± 10.1	<0.0001

Table 4
Relationship between baseline serum uric acid and insulin sensitivity in adults

Type 1 diabetes	Ln SUA	Quartile 1 of SUA	Quartile 2 of SUA	Quartile 3 of SUA	Quartile 4 of SUA
	$\beta^* \pm SE$ P-Value	Least square Mean $\pm$ SE	Least square Mean $\pm$ SE	Least square Mean $\pm$ SE	Least square Mean $\pm$ SE
eIS (unadjusted)	-1.90 ± 0.34 P < 0.0001	4.53 ± 0.12	4.49 ± 0.14	4.15 ± 0.16	4.13 ± 0.22
eIS (adjusted for model 1: age, sex, BMI, LnSCr)	-0.86 ± 0.35 P = 0.0155	$4.45 \pm 0.09^{**}$	$4.55 \pm 0.11^{**}$	4.25 ± 0.13	3.88 ± 0.19
eIS (adjusted for model 2: model 1, SBP, duration, LDL-c, HDL-c, glucose and current smoking)	-0.91 ± 0.33 P = 0.0063	$4.33 \pm 0.11^{**}$	4.31 ± 0.18	4.08 ± 0.13	3.79 ± 0.18
Controls	Ln SUA	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	$\beta^* \pm SE$ P-Value	Least square Mean $\pm$ SE	Least square Mean $\pm$ SE	Least square Mean $\pm$ SE	Least square Mean $\pm$ SE
eIS (unadjusted)	-18.19 ± 0.96 P < 0.0001	$19.34 \pm 0.62^{\dagger}$	$17.78 \pm 0.51^{\dagger}$	$16.38 \pm 0.48^{\dagger}$	11.56 ± 0.42
eIS (adjusted for model 1: age, sex, BMI, LnSCr)	-10.96 ± 1.02 P < 0.0001	$17.91 \pm 0.44^{\dagger}$	$17.04 \pm 0.37^{\dagger}$	$15.38 \pm 0.34^{**}$	13.58 ± 0.31
eIS (adjusted for model 2: model 1, SBP, LDL-c, HDL-c, glucose and current smoking)	-5.99 ± 0.75 P < 0.0001	$16.65 \pm 0.36^{\dagger}$	$16.17 \pm 0.31^{\dagger}$	$15.39 \pm 0.29^{**}$	14.37 ± 0.28

* β -coefficient represents the difference in estimated insulin sensitivity (ISI) for every 1-unit difference, and where appropriate for every natural log difference in the independent variable.

** P < 0.05 compared with the 4th Quartile.

[†] P < 0.0001 compared with the 4th Quartile.