Correlates of serum uric acid concentration and association with hypertension status in type 1 diabetes

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Background

- Serum uric acid has been positively related to hypertension (HTN) in the general population (1-2), although clinical trial data suggest that uric acid lowering agents do not affect endothelial function, a potential mechanism for HTN development, in overweight/obese normotensive individuals (3).
- Surprisingly, an inverse association between uric acid and HTN was recently reported in a type 1 diabetes cohort study (CACTI) (4).

Results from the CACTI study

Regression of systolic (SBP) and diastolic blood pressure (DBP) on log serum uric acid

Final multivariable models	SBP $\beta \pm \text{SE}$ (p-value)	DBP $\beta \pm \text{SE}$ (p-value)
Controls	5.42 $\pm$ 2.60 (0.04)	2.18 $\pm$ 1.74 (0.21)
Type 1 diabetes	-8.64 $\pm$ 4.05 (0.03)	2.27 $\pm$ 2.77 (0.42)

Progression in blood pressure or initiation of anti-HTN medications in the 4th vs. 1st uric acid quartile

Final multivariable models	OR (95% CI)
Controls	1.23 (0.75–2.02)
Type 1 diabetes	0.99 (0.47–2.08)

Aims

- We, therefore, sought to assess correlates of serum uric acid concentration, and its association with both SBP and HTN, in a cohort of childhood-onset type 1 diabetes.

The Pittsburgh Epidemiology of Diabetes Complications study

- Historical, prospective cohort based on incident cases of childhood-onset type 1 diabetes (diagnosed <17 years of age):
 - Individuals were diagnosed, or seen within 1 year of diagnosis, at Children's Hospital of Pittsburgh (1950–1980)
- This cohort was first examined between 1986 and 1988 (mean age 28, diabetes duration 19 years)
 - Participants (n=658) were subsequently reexamined or surveyed biennially for up to 25 years (currently, a 30 year examination is ongoing)
- For these analyses, participants attending the 25 year follow-up assessment and with available serum were studied (n=175)

Methods

- HTN was defined as blood pressure $\geq 140/90$ mm/Hg or use of anti-HTN medications.
- Uric acid was determined according to the enzymatic procedure of Fossati et al. (5) using reagents from Beckman Coulter (Center Valley, PA).
- Multivariable linear and logistic models were constructed to assess the independent relationship between serum uric acid and SBP or HTN, respectively.

Correlates of serum uric acid

Variables	r (p-value)	Variables	r (p-value)
Age	0.25 (0.0005)	eGDR	-0.38 (<0.0001)
Duration	0.27 (0.0002)	HDL	-0.18 (0.02)
BMI	0.11 (0.14)	Non-HDL	0.14 (0.06)
WHR	0.39 (<0.0001)	Cholesterol	-0.005 (0.95)
SBP	0.24 (0.001)	Triglycerides	0.28 (<0.0001)
DBP	0.01 (0.85)	eGFR	-0.51 (<0.0001)
Pulse rate	0.05 (0.47)	A/C ratio	0.43 (<0.0001)
HbA1c	0.03 (0.65)	WBC count	0.12 (0.11)
Insulin/weight	0.08 (0.28)		

Distribution of uric acid by HTN

Distribution of uric acid by sex

Independent correlates of uric acid (model R²=0.50)

	β (st. error)	p-value
Duration	0.01 (0.01)	0.45
Female gender	-0.88 (0.16)	<0.0001
BMI	0.003 (0.02)	0.85
HbA1c	-0.05 (0.05)	0.40
HTN status	0.14 (0.17)	0.39
HDLc	-0.0003 (0.004)	0.95
Non-HDLc	0.005 (0.002)	0.03
A/C ratio	0.002 (0.0007)	0.02
eGFR	-0.03 (0.004)	<0.0001
WBC count	0.01 (0.04)	0.75
ACE/ARB	0.05 (0.17)	0.74
LDL lipid meds	0.15 (0.17)	0.38

References

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Descriptive characteristics by HTN

	Normotensive (n=116)	Hypertensive (n=59)	p-value
Age (yrs)	50.3 (7.1)	53.3 (7.6)	0.01
T1D duration (yrs)	41.9 (6.4)	44.8 (7.2)	0.008
Female (% , n)	52.6 (61)	50.8 (30)	0.83
BMI (kg/m ²)	26.4 (23.8, 30.6)	29.5 (26.3, 33.0)	0.001
Waist to hip ratio	0.86 (0.09)	0.91 (0.08)	0.002
Ever smoker (% , n)	34.5 (40)	42.4 (25)	0.31
HbA _{1c} (%)	8.11 (7.4, 9.0)	7.9 (7.0, 9.0)	0.25
Insulin dose / weight	0.55 (0.39, 0.69)	0.56 (0.41, 0.72)	0.63
SBP (mmHg)	112 (102, 120)	120 (114, 140)	<0.0001
DBP (mmHg)	65 (59, 72)	65 (58, 75)	0.96
BP meds (% , n)	0.0 (0)	86.4 (51)	<0.0001
Pulse (beats/min)	76 (68, 80)	72 (64, 80)	0.31
HDLc (mg/dL)	60 (47, 75)	59 (46, 72)	0.41
Non-HDLc (mg/dL)	118 (97, 139)	105 (91, 139)	0.22
Lipid meds (% , n)	39.7 (46)	61.0 (36)	0.007
Statin use (% , n)	38.8 (45)	57.6 (34)	0.02
ACE/ARB use (% , n)	25.0 (29)	55.9 (33)	<0.0001
Urinary A/C ratio	10.2 (6.0, 19.9)	16.5 (8.4, 60.0)	0.01
eGFR (mL/min/1.73 m ²)	81.9 (19.9)	75.4 (23.7)	0.06
WBC count x10 ³ /mm ³	6.0 (5.2, 7.3)	6.3 (5.1, 7.7)	0.47
Ser. uric acid (mg/dL)	4.2 (3.4, 5.2)	4.7 (4.0, 5.8)	0.02

Regression models for SBP

	Model 1 β estimate $\pm$ S.E. (p-value)	Model 2 β estimate $\pm$ S.E. (p-value)
Serum uric acid	1.94 $\pm$ 0.94 (p=0.04)	1.15 $\pm$ 0.97 (p=0.24)
Duration	0.46 $\pm$ 0.18 (p=0.01)	0.42 $\pm$ 0.18 (p=0.02)
Urinary A/C ratio		0.02 $\pm$ 0.008 (p=0.005)
R ²	0.073385	0.113680

Model 1 allowed for diabetes duration, sex, and serum uric acid
Model 2 allowed for variables included in Model 1, plus HbA_{1c}, HDLc, non-HDLc, urinary A/C ratio, and eGFR

Logistic regression models for HTN status (n=175; 59 HTN cases)

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Uric acid	1.26 (0.97, 1.64, p=0.08)	1.28 (0.98–1.65, p=0.06)
Duration	1.05 (1.00, 1.11)	Not selected
Lipid medications		2.12 (1.10–4.09)
AIC	219.701	219.018

Model 1 allowed for diabetes duration, sex, and serum uric acid
Model 2 allowed for variables included in Model 1, plus HbA_{1c}, HDLc, non-HDLc, urinary A/C ratio, eGFR, and lipid medication use

Conclusions

- Female gender, non-HDL cholesterol, eGFR, and A/C ratio were independent correlates of serum uric acid.
- Serum uric acid was positively associated with HTN status but not SBP.
- We were thus unable to confirm the reported inverse association between uric acid and HTN prevalence in type 1 diabetes.