Urinary angiotensinogen and urinary sodium are associated with blood pressure in normoalbuminuric diabetic children.

Jolanta Sołtysiak, Bogda Skowrońska, Witold Stankiewicz, Piotr Fichna, Maria Lewandowska - Stachowiak , Magdalena Silska – Dittmar,
Danuta Ostalska - Nowicka, Jacek Zachwieja; Department of Pediatric Cardiology and Nephrology, Poznan University of Medical Sciences, Poland; jsoltysiak1@gmail.com

Bacground

The activation of intrarenal renin-angiotensin system (RAS) had a potential role in the mechanism and progression of diabetic kidney disease (DKD). Angiotensionogen (AGT) is the only known substrate for renin, which is the rate-limiting enzyme of the RAS. AGT is synthesized in the liver and proximal tubule, while urinary AGT (uAGT) is derived only from the kidneys and reflects intrarenal activation of RAS. In diabetic rats overexpression of AGT in the proximal tubule stimulated by hyperglycemia leads to tubular apoptosis, tubulointerstitial fibrosis and hypertension (HA). HA may accelerate the progression of DKD. AGT is important in the control of arterial pressure and renal sodium excretion.

The aim of this study was to evaluate the association of blood pressure with uAGT and urinary sodium excretion (uNa) in children with type 1 diabetes mellitus.

Methods

The study group consisted of 52 patients (28 males and 24 females) with a mean age of 14,39±2,49 years. All patients had eGFR above 90 ml/min/1.73m^2 and normal urinary albumin excretion (<30 mg/g) defined by the albumin/creatinine ratio (ACR). Blood pressure (BP) was assessed by 24-hour ambulatory blood pressure monitoring. Patients were considered as hypertensive, if their MAP, systolic, and diastolic BP was above 95th percentile regardless of BP load and dipping status. Prehypertensive children (preHA) showed BP below 95th percentile, while normal BP (nBP) was recognized below 90th percentile. AGT was measured in urine using an enzyme-linked immunosorbent assay commercially available kit. (Uscn Life Science Inc., USA). To avoid differences in spot urine, AGT was corrected for urinary creatinine. The control group consisted of 20 healthy, age and gender matched children. Nonparametric testing was used in statistical analysis.

Results

Grupa The patients showed significantly increased uAGT values with respect to controls (0.089±0.30 vs. 0.00±0.00ng/mg). The significant increase of uAGT was observed even in prehypertensive patients (table 1). uAGT levels showed positive correlation with BP values, both 24-hour systolic (r=0.538; p<0.001) and diastolic (r=0.485; p<0.001) blood pressure, as well as with mean arterial pressure (r=0.594; p<0.001). uNa values demonstrated negative correlation with systolic (r=-0.346; p=0.012) and mean arterial pressure (r=-0.293; p=0.035). There was negative correlation between levels of uNa and uAGT (r=-0.379; p=0.009). Only uNa showed negative correlation with ACR (r=-0.329; p=0.008) and eGFR (r=-0.338; p=0.011).

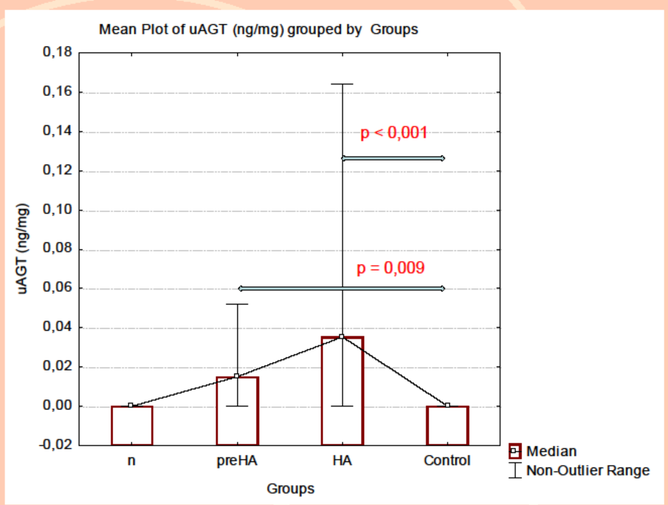

Figure 1. The comparison of uAGT in diabetic children to controls by blood pressure groups.

Table 1. The demographic and clinical data of the study group and controls

	Diabetes, n=52		Controls, n=20		p
	median	range	median	range	
uAGT (ng/mg)	0.00	1.76	0.00	0.00	0.015
Age (yr)	14.56	8.73	12.08	10.61	NS
RBMI (%)	104,7	15.96	101,81	16,66	NS
eGFR (ml/min/1.73m2)	111.44	140.06	101.27	83.99	NS
HbA1c (%)	7.95	9.00	5.45	0.80	<0.001
ACR (mg/g)	8.09	24.46	6.25	7.61	NS
uNa (mmol/l)	100.95	235.10	102.80	141.70	NS
sNa (mmol/l)	140.50	14.00	139.50	6.00	NS
FE_{Na}	0.33	1.06	0.25	0.48	NS

p – confidence level; NS – non-significant; na – not applicable; SD – standard deviation; uAGT – urinary AGT corrected for urinary creatinine (ng/mg); uNa – urinary sodium; sNa: serum sodium; RBMI - relative body mass index

Table 2. The comparison of diabetic children to controls by blood pressure groups.

	nBP; n=28		preHA; n=7		HA; n=17		Controls		p*	p**	p***
	median	range	median	range	median	range	median	range			
uAGT (ng/mg)	0.00	1.76	0.04	0.88	0.02	0.35	0.00	0.00	NS	0.009	<0.001
eGFR (ml/min/1.73m²)	105.77	83.52	105.77	45.54	122.04	134.22	101.27	83.99	NS	NS	NS
ACR (mg/g)	6.12	23.79	7.92	20.38	12.81	24.28	6.25	7.61	NS	NS	NS
uNa (mmol/l)	112.00	214.00	91.50	162.10	83.15	143.50	102.80	141.70	NS	NS	NS
sNa (mmol/l)	141.00	14.00	138.00	8.00	140.00	10.00	139.50	6.00	NS	NS	NS
FE_{Na}	0.40	0.87	0.51	0.63	0.22	0.58	0.25	0.48	NS	NS	NS

p* - confidence level between nBP and Controls; p** - confidence level between preHA and Controls; p*** - confidence level between HA and Controls; nBP – normal blood pressure; preHA – prehypertensive; HA – hypertensive; uNa – urinary sodium; sNa: serum sodium; SD – standard deviation; uAGT – urinary AGT corrected for urinary creatinine (ng/mg)

Table 3. The correlations of uAGT and uNa values with blood pressure and clinical parameters in the diabetic group.

	uAGT (ng/mg)	uNa (mmol/l)
24S	r=0.538 p<0.001	r=-0.346 p=0.012
24R	r=0.485 p<0.001	NS
24MAP	r=0.594 p<0.001	r=-0.293 p=0.035
D/N ratio	r=-0.279 p=0.042	r=0.419 p=0.002
diabetes duration (yr)	NS	r=-0.401 p=0.003
eGFR (ml/min/1.73m2)	NS	r=-0.338 p=0.011
HbA1c (%)	NS	r=-0.334 p=0.009
ACR (mg/g)	NS	r=-0.329 p=0.008
uNa (mmol/l)	r=-0.379 p=0.009	na
sNa (mmol/l)	NS	NS
FE_{Na}	r=-0.337 p=0.006	na

p – confidence level; NS – non-significant; na – not applicable; D/N ratio - the ratio between day and night (D/N) BP for MAP; ; uAGT – urinary AGT corrected for urinary creatinine (ng/mg); uNa – urinary sodium; sNa: serum sodium

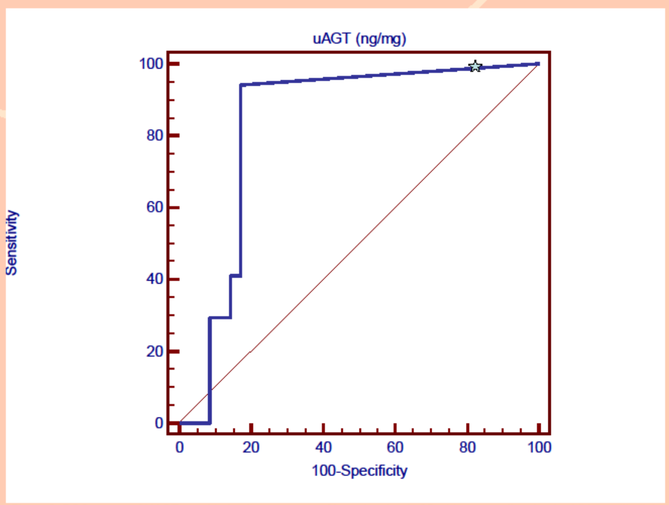

Figure 2. ROC curves of UAGT considering the presence of hypertension (≥ 95pc) in normoalbuminuric children with diabetes as status variable. The AUC for uAGT was 0,833 (CI 0,704 – 0,922). The best cutoff value for the identyfication of hypertension in diabetes was found to be above 0 ng/mg with a sensibility of 94,12 (CI 71.3 – 99.9) and a specificity of 82,86 (CI 68.4 – 93.4).

Table 4. ROC analysis of uAGT values

uAGT (ng/mg)	Sensitivity (95% CI)	Specificity (95% CI)	+LR	-LR
≥0	100.00 (80.5 – 100.0)	0.00 (0.0 – 10.0)	1.00	-
>0*	94.12 (71.3 – 99.9)	82.86 (68.4 – 93.4)	5.49	0.071
>0.03	41.18 (18.4 – 67.1)	82.86 (68.4 – 93.4)	2.40	0.71
>0.353	0.00 (0.0 – 19.5)	91.43 (76.9 – 98.2)	0.00	1.09
>1.7591	0.00 (0.0 – 19.5)	100.00 (90.0 – 100.0)	-	1.00

Best cutoff value for the identyfication of hypertension in normoalbuminuric children with diabetes: >0mg/mg.
Area under the ROC curve = 0,833; standard error = 0,0602; 95% confidence interval = 0,704 – 0,922.
+LR = positive likelihood ratio; -LR = negative likelihood ratio. *Best uAGT cutoff value.

Conclusions

- Increase in urinary AGT precedes the hypertension in diabetic children.
- Decreasing levels of sodium excretion seems to be involved in the development of HA and early renal injury.
- Both uAGT and uNa are associated with blood pressure in normoalbuminuric diabetic children.

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Jolanta Soltysiak
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