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Transient albuminuria in the setting of short-term severe hyperglycemia in type 1 diabetes

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Abstract

In a cohort of 1817 children with type 1 diabetes (T1D), short-term hyperglycemia was associated with transient albuminuria (11 % during new-onset T1D without diabetic ketoacidosis (DKA), 12 % during/after DKA, 6 % during routine screening). Our findings have implications regarding future risk of diabetic kidney disease and further investigation is needed.

Keywords

Type 1 diabetes; Diabetic ketoacidosis; Urine albumin-to-creatinine ratio

1. Introduction

Microalbuminuria is the earliest manifestation of kidney dysfunction in people with diabetes and a key risk factor for progression to diabetic kidney disease (DKD). Although chronically elevated hemoglobin A1c (HbA1c) is known to increase long-term risk of microalbuminuria,[1] acute changes in glomerular function resulting from exposure to short-term severe hyperglycemia have not been documented. We recently identified an association between acute kidney injury during episodes of diabetic ketoacidosis (DKA) and development of microalbuminuria in children with type 1 diabetes (T1D).[2] Within this

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CRediT authorship contribution statement

Jia Xin Huang: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Timothy Copeland:** Writing – review & editing, Validation, Formal analysis. **Casey E. Pitts:** Writing – review & editing, Data curation. **Sage R. Myers:** Writing – review & editing, Data curation. **Marissa J. Kilberg:** Writing – review & editing, Data curation. **Elaine Ku:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Nicole Glaser:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors have no relevant conflict of interests to disclose.

cohort, we observed high frequency of transiently elevated urine albumin-to-creatinine ratios (uACR) after episodes of DKA. In this analysis, we aimed to characterize the association between states of short-term severe hyperglycemia and transiently elevated uACR.

2. Material and methods

We performed a retrospective analysis of longitudinal uACR data from children with T1D at Children's Hospital of Philadelphia (CHOP). We included data from patients with T1D who were < 18 years old at the time of diagnosis; had ≥1-year follow-up after T1D diagnosis; and had ≥1 uACR measurement. All available uACR values were recorded up to the time of initiation of treatment for albuminuria, if applicable. The study was approved by the CHOP institutional review board.

The timing of uACR measurement was determined in relation to the date of T1D diagnosis and DKA episodes and classified as 1) new onset T1D if the date of measurement was within seven days of T1D diagnosis; 2) DKA if the date of measurement was within seven days of a DKA episode; and 3) routine screening if the measurement was neither shortly after TID diagnosis T1D nor during/after a DKA episode. The 7-day cutoff was chosen to encompass the typical duration of hospitalization for new onset T1D or DKA (≤7 days), during which time the uACR measurements were obtained. Mean hemoglobin A1c (HbA1c) levels for each patient were calculated as the average of all HbA1c measurements since diagnosis.

uACR values were categorized following the recommendations of the 2022 Kidney Disease Improving Global Outcomes guidelines for chronic kidney disease.[3] Values of uACR <30 mg/g were categorized as normal/mildly increased (A1); moderately increased 30–300 mg/g (A2 - previously referred to as microalbuminuria); and severely increased >300 mg/g (A3 - previously macroalbuminuria).[3] Abnormal uACR measurements for each patient were further classified as transiently abnormal, persistently abnormal, or unconfirmed (no subsequent uACR to confirm the previous value). Abnormal A2 or A3 albuminuria values followed by an A1 albuminuria value were classified as transiently abnormal if these measurements occurred within 90 days. Albuminuria was classified as persistently abnormal if there were two abnormal values that were >90 days apart. Transiently abnormal uACR was the primary outcome of interest.

Descriptive statistics were computed using chi-square tests to compare characteristics between patients who never had an abnormal uACR measurement with those who had ≥1abnormal uACR measurement, and to compare patient characteristics across uACR categories. To examine associations between the setting of sample collection (at new onset of T1D, during/shortly after DKA, routine outpatient screening) and risk of transiently abnormal uACR, we performed mixed logistic regression with clustering to account for repeated measurements from the same individuals. Age, sex, diabetes duration, and setting of the measurement were included as covariates in these models. Samples with unconfirmed albuminuria were excluded from the main analysis, however, we conducted a sensitivity analysis including these samples. All data analyses were performed using STATA software version 16.1 (StataCorp, LLC, College Station TX).

3. Results

1817 patients were included with mean age at T1D diagnosis of 9.7 ± 4.2 years and mean follow-up time of 3 years ±3 years (Table 1). Most patients were male (56 %) and non-Hispanic White (71 %). Mean HbA1c since T1D diagnosis was 8.1 % ± 1.4 %. Compared to patients who never had abnormal uACR measurements, patients with ≥1 abnormal uACR measurement had higher HbA1c levels and were more likely to be female (Table 1).

7258 uACR measurements were collected with most values obtained during routine screening (Table 2). More abnormal uACR measurements were obtained during new onset T1D (11 % transiently abnormal, 2 % persistently abnormal) and DKA (12 % transiently abnormal, 4 % persistently abnormal) compared to those obtained during routine screening (6 % transiently abnormal, 3 % persistently abnormal). The majority of the abnormal measurements were in the moderately increased A2 albuminuria range. We observed differences in likelihood of having transient albuminuria (percent of samples from patients in each racial/ethnic group: Asian 6.5 %, Black 4.3 %, Hispanic 7.6 %, Non-Hispanic White 7.4 %, and Other/Multi-Racial 6.7 %) and persistent albuminuria (Asian 0 %, Black 4.6 %, Hispanic 3.8 %, Non-Hispanic White 3.2 %, and Other/Multi-Racial 1 %) among measurements from children of different racial/ethnic groups.

In multivariable analyses, the odds of having transiently abnormal uACR was higher in girls vs. boys (OR 1.44, 95 % CI 1.17–1.78) and when uACR measurements were obtained during/after DKA (OR 2.15, 95 % CI 1.50–3.07) compared to routine screening (Table 3). The odds of transient albuminuria were lower with every 1-year increase in age at measurement (OR 0.98, 95 % CI 0.95–1.00). Results were similar in sensitivity analyses when we included unconfirmed albuminuria in the transiently abnormal uACR group.

4. Discussion

Compared with children undergoing routine screening for albuminuria, children with DKA had higher odds of having transient albuminuria that normalized within 90 days. Female sex and younger age were also associated with a higher frequency of transient albuminuria.

While albuminuria is a key risk factor for development of diabetic kidney disease, regression of moderately increased uACR in patients with diabetes is not uncommon.[4–8] 50–60 % of adults with T1D who had moderate (A2) albuminuria at baseline were observed to have regression to normoalbuminuria during 7 years of follow-up.[5,6] Similarly, in children, the Oxford regional prospective study found that children with T1D who had albuminuria had high rates (51 %) of regression to normal/mildly increased (A1) albuminuria after 5 years.[7] An even higher proportion (86.2 %) of regression of albuminuria was observed among children and adolescents with T1D after 7 years of follow up in the T1D SEARCH study.[8] In these studies, only 5–12 % of the children and adolescents who had regression of albuminuria were started on treatment with angiotensin converting enzyme inhibitors. None of those studies specifically evaluated the frequency of albuminuria following episodes of short-term severe hyperglycemia. In our study, the frequency of transient albuminuria detected during/shortly after DKA was double that of transient albuminuria identified

during routine screening (Table 2). A similar incidence of transient albuminuria was also observed at new onset T1D without DKA, although these findings did not achieve statistical significance.

The association between DKA episodes and albuminuria has been previously observed in a small cohort of nine children,[9] however, that study did not include comparison data from children undergoing routine albuminuria screening. Our study verifies these findings in a much larger pediatric cohort, using comparisons among groups defined by screening setting, and with a longer follow-up period. Tubular dysfunction has been identified during episodes of DKA[10,11] and among patients with poor glycemic control.[12] Our findings suggest that this tubular dysfunction may be associated with transient albuminuria in some patients. Whether transient episodes of albuminuria are markers of irreversible kidney injury and greater long-term risk of DKD is unclear. Subsets of patients with type 1 and type 2 diabetes have been found to have histological evidence of DKD prior to development of albuminuria, suggesting that kidney injury may be present even in the absence of persistent albuminuria.[13]

Our finding that transient albuminuria was more common in girls than boys aligns with findings from other observational studies reporting higher rates of albuminuria among women.[7,14] Women may be more likely to have elevated uACR values due to lower urine creatinine excretion and differences in muscle mass.[15] While older age and longer duration of diabetes are associated with persistent albuminuria,[7,14,16] they were not found to be associated with transient albuminuria in our study.

Our study does have limitations due to the retrospective design. Markers of inflammation are not typically measured in children with T1D and therefore were not available in the medical records. It is unclear whether some patients in the cohort may have had inflammation not related to DKA (e.g., systemic infection or urinary tract infection), severe hypertension, orthostatic proteinuria, or other confounders that could contribute to transient albuminuria at the time of uACR measurements.[17,18] Data on body weight percentile, outpatient creatinine values, and family history of diabetes or kidney disease also were not available in the database.

In conclusion, children with T1D are more likely to have transient albuminuria if urine samples for ACR measurement are obtained during or shortly after a DKA episode. It is possible that short-term severe hyperglycemia may induce transient tubular dysfunction contributing to increased uACR. Additional investigation is needed to understand the implications of these findings and whether they indicate increased long-term risk of diabetic kidney disease. Clinicians should be aware that uACR measurements obtained during or shortly after DKA are more likely to be transiently abnormal, and results should be interpreted in light of these findings.

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Abbreviations:

DKA	diabetic ketoacidosis
uACR	urine albumin-to-creatinine ratio
DKD	diabetic kidney disease
T1D	type 1 diabetes
HbA1c	hemoglobin A1c

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Table 1

Characteristics of patients included for study.

Characteristics	All *N* = 1817	Never had abnormal uACR *N* = 1592	≥1 abnormal uACR *N* = 225	*p*-Value
Age (years) at diagnosis, mean (SD)	9.7 (4.2)	9.6 (4.0)	10.0 (4.0)	0.13
Female	805 (44 %)	678 (43 %)	127 (56 %)	<0.001
Race				0.24
Asian	15 (1 %)	14 (1 %)	1 (0 %)	
Black	293 (16 %)	265 (17 %)	28 (12 %)	
Hispanic	39 (2 %)	31 (2 %)	8 (4 %)	
Non-Hispanic White	1298 (71 %)	1130 (71 %)	168 (75 %)	
Other/Multi-Racial	172 (10 %)	152 (10 %)	20 (9 %)	
Mean HbA1c (%), mean (SD)	8.1 (1.4)	8.1 (1.4)	9.2 (1.4)	0.18
Years of follow-up, mean (SD)	3.4 (2.8)	3.4 (2.8)	3.6 (2.8)	0.47

Characteristics are provided as n (column %) unless otherwise indicated mean (SD). *p*-value displayed is comparing patients who never had an abnormal uACR measurements with patients who had at least 1 abnormal uACR measurements.

Abbreviations: HbA1c = hemoglobin A1c, uACR = urine albumin-creatinine ratio.

Table 2

Characteristics by urine albumin to creatinine ratio (uACR) categories.

	Normal	Transiently abnormal	Persistently abnormal	Unconfirmed	*p*-Value
	***N* = 6438**	***N* = 498**	***N* = 249**	***N* = 73**	
Age at measurement, years, mean (SD)	12.8 (4.0)	12.4 (3.7)	13.1 (3.4)	14.1 (3.6)	0.003
Female	2845 (44 %)	268 (54 %)	144 (58 %)	37 (51 %)	<0.001
Race					0.02
Asian	58 (1 %)	4 (1 %)	0 (0 %)	0 (0 %)	
Black	982 (15 %)	47 (9 %)	50 (20 %)	14 (19 %)	
Hispanic	116 (2 %)	10 (2 %)	5 (2 %)	0 (0 %)	
Non-Hispanic White	4743 (74 %)	396 (80 %)	170 (68 %)	53 (73 %)	
Other/Multi-Racial	539 (8 %)	41 (8 %)	24 (10 %)	6 (8 %)	
Mean HbA1c (%), mean (SD)	8.1 (1.3)	8.2 (1.3)	8.7 (1.4)	8.7 (1.8)	<0.001
Timing of uACR measurement					<0.001
Routine Screening	6031 (94 %)	438 (88 %)	230 (92 %)	61 (84 %)	
New-onset T1D[a]	73 (1 %)	9 (2 %)	2 (1 %)	1 (1 %)	
During/after DKA	334 (5 %)	51 (10 %)	17 (7 %)	11 (15 %)	
Albuminuria level					<0.001
Moderate increased (A2)	N/A	448 (90 %)	215 (86 %)	62 (85 %)	
Severely increased (A3)	N/A	50 (10 %)	34 (14 %)	11 (15 %)	

Characteristics are provided as n (column %) unless otherwise indicated by mean (SD). Values of uACR <30 mg/g follow 2022 KDIGO guidelines. Abnormal A2 or A3 albuminuria value followed by an A1 albuminuria value was classified as transiently abnormal if they were within 90 days apart and classified as persistently abnormal if beyond 90 days. If the last uACR measurement for a patient was in the A2 or A3 range, it was classified as unconfirmed.

Abbreviations: uACR = urine albumin-creatinine ratio, T1D = type 1 diabetes, DKA = diabetic ketoacidosis.

[a]Not in DKA.

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Table 3

Multivariable analysis of factors associated with the odds of transiently abnormal uACR.

Variables	Transiently abnormal uACR		Transiently abnormal/unconfirmed abnormal uACR	
	OR (95 % CI)	*p*-Value	OR (95 % CI)	*p*-Value
Age at measurement (per 1-year increase)	0.98 (0.95–1.00)	0.04	0.99 (0.96–1.01)	0.32
Female (vs. male)	1.44 (1.17–1.78)	<0.001	1.41 (1.16–1.71)	0.001
Years of follow-up (per 1-year increase)	1.02 (0.98–1.06)	0.34	0.98 (0.95–1.02)	0.38
Timing of uACR measurement				
Routine Screening	Reference		Reference	
New-onset T1D[a]	1.95 (0.93–4.09)	0.08	1.79 (0.88–3.63)	0.11
During/after DKA	2.15 (1.50–3.07)	<0.001	2.34 (1.68–3.25)	<0.001

Mixed logistic regression analysis including only transiently abnormal uACR as the outcome (middle column) and transiently abnormal plus unconfirmed abnormal uACR (sensitivity analysis-right column). All analyses were clustered by patient to account for multiple uACR measurements from the same individual.

Abbreviations: T1D = type 1 diabetes, DKA = diabetic ketoacidosis, uACR = urine albumin-to-creatinine ratio.

[a]Not in DKA.