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Occurrence of microalbuminuria in young people with Type 1 diabetes: importance of age and diabetes duration

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Abstract

Aims—To determine the occurrence of microalbuminuria in young people with Type 1 diabetes mellitus followed prospectively for 2 years and to relate the presence of persistent elevations in urinary albumin excretion (UAE) to age, diabetes duration, puberty and other factors.

Methods—During a 2 year period, random urine samples were obtained from 471 patients, aged 8–18 years (mean $\pm$ SD 12.9 ± 2.3 years) with Type 1 diabetes duration 5.6 ± 3.0 years, as part of routine clinical care. Urine albumin and creatinine concentrations were measured in 1310 samples (median, 3 samples per patient) and the albumin:creatinine ratio was calculated (in micrograms albumin per milligram creatinine). Height, weight, blood pressure (BP), glycated haemoglobin (HbA_{1c}), blood glucose monitoring frequency and Tanner staging were collected from patients' medical records.

Results—Twenty-three per cent of patients had one or more sample with elevated UAE (≥ 20 μ g/mg) and 9.3% had persistent elevations (≥ 2 samples ≥ 20 μ g/mg). Those with and without persistent microalbuminuria did not differ significantly in age, diabetes duration, z-score for body mass index, pubertal status or BP percentile. Ten per cent of children <13 years old and 9% of children ≥ 13 years old had persistent microalbuminuria. Persistent microalbuminuria was significantly associated with diabetes duration only in older children (duration 0.5–3 years, 4%; 4–6 years, 8%; ≥ 7 years, 14%; $P = 0.02$, trend test). Mean HbA_{1c} over the 2 years was $8.7 \pm 1.2\%$. In a logistic regression model, mean HbA_{1c} was the only significant predictor of persistent microalbuminuria (odds ratio 1.3, 95% confidence interval 1.0–1.6, $P = 0.05$).

Conclusions—Microalbuminuria in older children with Type 1 diabetes is likely to be clinically significant. In younger children, it may reflect functional, reversible renal changes. Longitudinal analysis is needed to confirm the probable transient nature of microalbuminuria in young patients with Type 1 diabetes.

Keywords

children; glycated haemoglobin; microalbuminuria; puberty; Type 1 diabetes mellitus

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Competing interests

None to declare.

Introduction

Diabetic nephropathy is a major late complication of Type 1 diabetes mellitus (Type 1 DM) associated with significant morbidity and mortality [1–3]. Microalbuminuria is considered to be an early sign of diabetic renal disease. It precedes persistent proteinuria and represents a potentially reversible stage of diabetic nephropathy.

Approximately 30–40% of persons with Type 1 DM develop microalbuminuria [4,5]. Less than half the patients with microalbuminuria will progress to overt proteinuria over the next decade, while the microalbuminuria will either regress or remain stable in a substantial proportion of the patients [6]. In adults, microalbuminuria is associated with an increased risk for cardiovascular disease and early mortality [7].

Microalbuminuria occurs in association with poor glycaemic control, elevated blood pressure and longer diabetes duration. In reports of children and adolescents with Type 1 DM, the prevalence of microalbuminuria varies from 10 to 40%. However, only 5–10% of young people demonstrate persistent elevations in urinary albumin excretion (UAE) [8–10]. The high rate of regression and transient nature of microalbuminuria in young people with Type 1 DM has been attributed to changing renal haemodynamics associated with pubertal growth and development [6,9,11,12].

Current recommendations from the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes regarding screening for microalbuminuria in young people with Type 1 DM suggest annual testing after 10 years of age and after diabetes duration of 5 years [13,14]. Recommendations include treatment with angiotensin-converting enzyme (ACE) inhibitors for young people with persistent elevations in UAE and no other recognized cause of kidney disease. It is important to assess factors related to the development of microalbuminuria in young people with Type 1 DM in order to identify whether such changes are due to underlying renal pathology or may be related to functional changes. Renal haemodynamic changes may occur during pubertal growth and development or may reflect uncontrolled diabetes and glycaemic variability, both of which are common during puberty.

In the present investigation, we determined the occurrence of microalbuminuria in a large cohort of young people with Type 1 DM followed prospectively for 2 years and related the presence of persistent elevations in UAE to age, duration of diabetes, pubertal status and other clinical factors.

Patients and methods

Young people with Type 1 DM ($n = 471$) were followed prospectively for 2 years at a tertiary diabetes centre. Patients' medical records were reviewed for the following eligibility criteria: age 8–18 years; Type 1 DM duration ≥ 6 months; residence in New England; and routine diabetes care at the Joslin Diabetes Center. One patient with pre-existing renal disease was excluded from analyses. The study protocol was approved by the Institutional Review Board, and written informed consent/assent was obtained from parents/young people.

Random urine specimens were collected at medical visits as part of patients' routine clinical care. Urine albumin and creatinine concentrations were measured and the urine albumin:creatinine ratio was calculated (in micrograms albumin per milligram creatinine) [15]. [To convert from μg albumin/mg creatinine to mg albumin/mmol creatinine, divide by 8.84.] Urine albumin concentration was measured by immunonephelometry with N Albumin kits (Behring, Somerville, NJ, USA). Normal UAE was defined as $<20 \mu\text{g}/\text{mg}$ [15]. Height, weight, blood pressure (BP), glycated haemoglobin ($\text{HbA}_{1\text{c}}$), insulin dose, blood glucose monitoring frequency and Tanner (T) staging were obtained from patients' medical records.

Twenty-nine patients did not have any Tanner staging data during the 2 year period. For these patients, pubertal development was estimated using age (T1 males <12.2 years, females <10.9 years; T2–T4 males 12.2–15 years, females 10.9–15 years; and T5 males and females >15 years) [16]. Age- and sex-adjusted body mass index (zBMI) was calculated from height and weight [17]. Glycated haemoglobin was measured by high-performance liquid chromatography standardized to the Diabetes Control and Complications Trial assay (reference range, 4.0–6.0%; Tosoh Bioscience, South San Francisco, CA, USA). Values of HbA_{1c} and BP measurements from the 2 year period were averaged to create 2 year mean exposure variables for each person. Age-, sex- and height-adjusted BP percentiles were also calculated.

Statistical analyses were performed using SAS software (version 9.2, Cary, NC, USA). Means $\pm$ SD or medians with interquartile ranges are presented. Analyses included Student's unpaired *t* tests, χ^2 analyses and tests for trend. In order to consider multiple variables and control for potential confounders, we performed logistic regression with persistent microalbuminuria as the dependent variable. Values of $P \leq 0.05$ were considered statistically significant.

Results

Study population

Four hundred and seventy-one young people with Type 1 DM (45% male) comprised the study sample. Characteristics of the cohort at the time of each patient's first urine collection appear in Table 1. Mean age of the sample was 12.9 ± 2.3 years and mean duration of diabetes was 5.6 ± 3.0 years. Pubertal status varied, with 24% prepubertal (T1), 43% pubertal (T2–T4) and 33% postpubertal (T5). Mean zBMI was 0.71 ± 0.75 . Mean systolic and diastolic BP percentiles were 48 ± 27 and 58 ± 21 , respectively. The mean 2 year average HbA_{1c} was $8.7 \pm 1.2\%$.

Urine samples

A total of 1310 urine samples were collected during the 2 year period, with a median of three samples per patient. The median time between samples was 9 months (interquartile range, 7.0–12.5 months). Only 71 of the 471 patients (15%) provided a single urine sample. Notably, 86% of the 1310 urine samples had an albumin:creatinine ratio <20 $\mu\text{g}/\text{mg}$; 8% of samples were between 20 and 50 $\mu\text{g}/\text{mg}$ and 6% were >50 $\mu\text{g}/\text{mg}$ (see Fig. 1). Of the 471 patients, 77% ($n = 364$) had normal UAE (<20 $\mu\text{g}/\text{mg}$) in all samples and 23% ($n = 107$) had elevated UAE ($\geq 20 \mu\text{g}/\text{mg}$) in at least one urine sample. Of the 107 patients with elevated UAE in at least one sample, 40% ($n = 43$) had persistently elevated UAE on an additional specimen during the 2 year period. Of the remaining 64 patients with elevated UAE in at least one sample, 60 had subsequent urine samples with normal UAE values during follow-up and were classified as not having persistent microalbuminuria. Of the four patients who did not provide a second urine sample, three patients (females aged 10, 12 and 14 years) had only a modest elevation (UAE $\leq 35 \mu\text{g}/\text{mg}$) in their initial sample and were thus not classified as having persistent microalbuminuria. The fourth patient was a 15-year-old male with a single UAE of 512 $\mu\text{g}/\text{mg}$. This patient had subsequent elevated values beyond the 2 year period and was started on ACE inhibition and was therefore categorized as having persistent microalbuminuria for this analysis. Thus, a total of 44 patients (9.3% of the sample) were categorized as having persistent microalbuminuria.

Factors associated with elevated UAE

To determine the clinical correlates of elevated UAE, we compared patients without persistent elevations in UAE ($n = 427$) with those having persistently elevated UAE ($n = 44$; see Table 1). There were no statistically significant differences between those without persistent microalbuminuria and those with persistent microalbuminuria regarding age (12.9 ± 2.3 vs. 12.8 ± 2.1 years), diabetes duration (5.5 ± 3.1 vs. 6.2 ± 2.8 years), zBMI (0.70 ± 0.75 vs. 0.81

± 0.75), pubertal status T2–T4 (43 vs. 48%), systolic BP percentile (48 ± 27 vs. 48 ± 28) or diastolic BP percentile (58 ± 21 vs. 59 ± 24). However, there was a higher percentage of females among those with persistent microalbuminuria than those without persistent microalbuminuria (75 vs. 52%, $P = 0.004$). In addition, 2 year mean HbA_{1c} was significantly higher in those with persistent microalbuminuria ($9.1 \pm 1.4\%$) than in those without ($8.7 \pm 1.2\%$, $P = 0.03$).

Impact of age and diabetes duration on UAE

To determine the impact of maturation and exposure to diabetes on UAE, we stratified patients according to age (8–12 and 13–18 years) and duration of Type 1 DM (0.5–3, 4–6 and ≥ 7 years) and analysed the occurrence of persistent microalbuminuria by these groups. Persistent microalbuminuria was found in 10% of 8- to 12-year-olds ($n = 25$ of 250) and 9% of 13- to 18-year-olds ($n = 19$ of 221; n.s.). The proportion of patients with persistent microalbuminuria did not differ significantly by duration group (0.5–3 years, 7%, $n = 11$ of 164; 4–6 years, 9%, $n = 16$ of 173; and ≥ 7 years, 13%, $n = 17$ of 134; $P = 0.21$); the trend was not significant ($P = 0.08$).

To assess the impact of diabetes exposure among younger and older children and adolescents, we determined the prevalence of persistent microalbuminuria according to diabetes duration in the 8- to 12-year-old young people and the 13- to 18-year-old young people. In the younger patients, the prevalence of persistent microalbuminuria was similar in all duration groups (9–11%; see Fig. 2). In the older patients, however, the prevalence of persistent microalbuminuria varied significantly by duration group. Persistent microalbuminuria occurred in 4% of those with 0.5–3 years duration, 8% of those with 4–6 years duration and 14% of those with ≥ 7 years duration ($P = 0.02$, test for trend).

In logistic models with persistent microalbuminuria as the outcome, the 2 year mean HbA_{1c} remained a significant independent predictor variable (odds ratio 1.3, 95% confidence interval 1.0–1.6; $P = 0.05$) after controlling for age, duration of diabetes, blood pressure, zBMI and daily insulin dose (in units/kg). Inclusion of an interaction term between age and duration failed to achieve significance, possibly due to a type II statistical error resulting from the relatively small number of patients with persistent microalbuminuria.

Discussion

In this cohort of 471 young people with Type 1 DM, we found elevated UAE in 23% of the sample, with isolated elevations in 13% and persistent microalbuminuria in 9.3%. These rates of microalbuminuria and persistent microalbuminuria are similar to rates reported by others. In the Oxford Regional Prospective Study of young people with Type 1 DM, the prevalence of elevated UAE was 13–26% and the prevalence of persistent UAE was 5% [9]. Several groups from Australia have reported prevalence rates of 6–18% for elevated UAE in youth [8,10]. In a Swedish cohort of 426 young patients with Type 1 DM, the investigators found a prevalence of microalbuminuria of 5.6% [18].

We calculated 2 year mean data for HbA_{1c} and blood pressure to assess exposure to factors known to be related to UAE. Not unexpectedly, elevated HbA_{1c} was significantly associated with persistent microalbuminuria in our sample, although blood pressure was not. The mean 2 year HbA_{1c} was 9.1% in the young people with persistently elevated UAE compared to 8.7% in those with normal UAE. Data from adolescents aged 13–17 years at entry into the Diabetes Control and Complications Trial demonstrate the importance of blood glucose control for the development of microvascular complications; a 40% risk reduction for the development of microalbuminuria was experienced in the intensively treated group compared with the conventionally treated group [19,20]. Interestingly, in our cohort, there were no differences in

age, diabetes duration, zBMI, pubertal status or BP percentile between those with and those without persistent microalbuminuria.

Puberty has also been studied as an independent risk factor for microalbuminuria, with data suggesting that the prepubertal duration of Type 1 DM might not be as significant a contributing factor for microalbuminuria as the postpubertal years [8]. In studies by Donaghue *et al.* [21] and Olsen *et al.* [22], prepubertal duration of Type 1 DM was not significantly associated with occurrence of microalbuminuria. In a small cohort from Hungary followed for 3 years, puberty was an independent risk factor for the development of microalbuminuria [23]. These studies that reported no effect of prepubertal duration of diabetes on the occurrence of elevated UAE may have had insufficient numbers of patients or may have been confounded by functional renal haemodynamic changes that may occur with puberty, leading to elevations in UAE independent of diabetes duration, as in our sample of 8- to 12-year-olds.

We found no difference in the occurrence of persistent microalbuminuria in younger (ages 8–12 years) compared to older (ages ≥ 13 years) children and adolescents, with prevalence rates of 10 and 9%, respectively. The significance of the higher percentage of females with persistent microalbuminuria is unclear, although consistent with previous literature [24]. Furthermore, there were no significant differences in the rates of persistent microalbuminuria across the diabetes duration groups (0.5–3, 4–6 and ≥ 7 years) when all young people, aged 8–18 years, were analysed together. However, duration of Type 1 DM was significantly related to persistent microalbuminuria in the older individuals but not in the younger children. In the older children in our study, the influence of pubertal growth and development was receding while the impact of diabetes exposure was emerging, marked by the increased occurrence of persistent microalbuminuria in those with longer diabetes duration. The lack of relationship between diabetes duration and persistent microalbuminuria among the younger patients seemed to arise from an excess of elevated UAE in young people undergoing pubertal growth and development and its attendant uncontrolled diabetes. Functional renal haemodynamic changes have been described in patients with new onset Type 1 DM who have experienced wide fluctuations in blood glucose levels that revert to normal within months upon institution of insulin therapy and improvement in glycaemic control [25,26].

Microalbuminuria in patients with Type 1 DM does not inevitably lead to overt proteinuria and end-stage renal disease. Many studies have shown regression to normoalbuminuria in 40–60% of patients. In a study of 400 adults with Type 1 DM and microalbuminuria, Perkins *et al.* found that only 19% developed overt proteinuria, while 60% displayed regression; HbA_{1c} <8.0%, lower systolic BP, and low cholesterol and triglyceride levels were independently associated with regression [6]. Studies in children and adolescents have demonstrated similar regression rates of 32–58% [27–29]. Steinke *et al.* followed 178 patients with Type 1 DM for 5 years; all patients were normoalbuminuric at baseline [11]. Of the 22 patients who met criteria for persistent microalbuminuria at some point during the follow-up period, 14 patients (64%) had reverted to normoalbuminuria and eight patients (36%) still had persistent microalbuminuria at the end of the study; treatment with ACE inhibitors was not a significant predictor of regression. Gorman *et al.* [29] found a 32% rate of regression over 6 years in adolescents who had microalbuminuria at baseline.

Our findings suggest that the significance of persistent elevations in UAE may vary according to age and/or pubertal status as noted by the difference in risk according to Type 1 DM duration. Younger patients with Type 1 DM experienced elevated UAE at the same rate regardless of diabetes duration, suggesting that elevated UAE in this age group may be linked to functional, transient haemodynamic alterations, possibly related to pubertal growth and development and/or uncontrolled diabetes. These elevations in UAE may be less likely to progress to persistent proteinuria and, thus, may not warrant clinical intervention other than optimizing glycaemic

control. In contrast, the older group demonstrated an increased occurrence of microalbuminuria according to diabetes duration, suggesting a relationship between diabetes exposure and elevated albumin excretion that may be more likely to progress to diabetic nephropathy. It is important to identify which young patients are likely to display true persistence and progression and thus warrant intervention such as blockade of the renin–angiotensin system.

This study aimed to determine the occurrence of microalbuminuria in a relatively large sample of young people with Type 1 DM and to assess the determinants of persistence over a 2 year period. The major limitations of our study are the lack of statistical power for some analyses and the lack of longitudinal data beyond the 2 years. Despite the relatively large study sample, the number of young people with persistent microalbuminuria was rather small. Thus, the analyses may be underpowered to identify clinically important factors predictive of microalbuminuria and renal complications. Longer follow-up of these patients is necessary to document regression or progression of microalbuminuria. Furthermore, we were not able to assess the impact of other diabetes complications (such as retinopathy) or the effect of clinical interventions (such as blockade of the renin–angiotensin system or intensification of glycaemic control) during the 2 year period.

Despite these limitations, our findings allow us to comment on the significance of the prepubertal years for the development of microalbuminuria. Diabetes duration was not related to elevated UAE in younger patients. However, duration appears to be linked to the occurrence of microalbuminuria in the older group, suggesting that overall diabetes exposure, including both pre- and postpubertal duration, contributes to persistent increases in UAE in older adolescents with Type 1 DM. Additional longitudinal studies are needed to confirm our observations and to determine the true rate of regression or progression of microalbuminuria in young people with Type 1 DM in order to direct therapeutic interventions to prevent the development of overt diabetic nephropathy.

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Abbreviations

ACE	angiotensin-converting enzyme
BP	blood pressure
DM	diabetes mellitus
HbA_{1c}	glycated haemoglobin
n.s.	not significant
UAE	urinary albumin excretion
zBMI	age- and sex-adjusted body mass index

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FIGURE 1.

Distribution of urinary albumin excretion values for all urine samples ($n = 1310$) collected during the 2 year period. The majority of urine albumin:creatinine values (51%) were ≤ 5 $\mu\text{g}/\text{mg}$. Only 14% of all values were above normal (≥ 20 $\mu\text{g}/\text{mg}$). (To convert from $\mu\text{g}/\text{mg}$ to mg/mmol , divide by 8.84.)

FIGURE 2.

Prevalence of persistent microalbuminuria according to age and Type 1 DM duration. For younger patients (aged 8–12 years), prevalence of persistent microalbuminuria did not differ by Type 1 DM duration group. For older patients (aged 13–18 years), there was a significant trend towards higher prevalence of persistent microalbuminuria with longer Type 1 DM duration (test for trend, $P = 0.02$). Black bars represent Type 1 DM duration ≤ 3 years; white bars, Type 1 DM duration 4–6 years; and grey bars, Type 1 DM duration ≥ 7 years.

Table 1

Baseline patient characteristics

	All patients (<i>n</i> = 471)	Patients without microalbuminuria (<i>n</i> = 427)	Patients with microalbuminuria (<i>n</i> = 44)	<i>P</i> value
Age (years)	12.9 ± 2.3	12.9 ± 2.3	12.8 ± 2.1	n.s.
Sex (% female)	55%	52%	75%	0.004
Pubertal stage (%)				
Tanner 1	24%	25%	14%	n.s.
Tanner 2–4	43%	43%	48%	
Tanner 5	33%	32%	39%	
zBMI (SDS)	0.71 ± 0.75	0.70 ± 0.75	0.81 ± 0.75	n.s.
Type 1 DM duration (years)	5.6 ± 3.0	5.5 ± 3.1	6.2 ± 2.8	n.s.
Blood glucose monitoring frequency (times per day)	3.4 ± 1.0	3.4 ± 1.0	3.4 ± 0.9	n.s.
Insulin regimen (% pump)	6%	6%	7%	n.s.
Number of injections per day (for patients on injection therapy)	2.8 ± 0.6	2.7 ± 0.6	2.8 ± 0.6	n.s.
Daily insulin dose (units/kg)	0.95 ± 0.24	0.94 ± 0.24	1.00 ± 0.18	0.04
Systolic BP percentile	48 ± 27	48 ± 27	48 ± 28	n.s.
Diastolic BP percentile	58 ± 21	58 ± 21	59 ± 24	n.s.
2 year mean systolic BP (mmHg)	109 ± 8	109 ± 8	109 ± 7	n.s.
2 year mean diastolic BP (mmHg)	67 ± 5	67 ± 5	68 ± 5	n.s.
2 year mean HbA _{1c} (%)	8.7 ± 1.2	8.7 ± 1.2	9.1 ± 1.4	0.03

Values are expressed as means ± SD or percentages.

BP, blood pressure; HbA_{1c}, glycated haemoglobin; n.s., not significant; SDS, standard deviation score; and zBMI, age- and sex-adjusted body mass index.