Natural History and Risk Factors for Microalbuminuria in Adolescents With Type 1 Diabetes

A longitudinal study

MONIQUE L. STONE, MBBS, FRACP[1,2]
MARIA E. CRAIG, MBBS, PHD, FRACP[2,3,4]
ALBERT K. CHAN, MAPPSTAT[3]
JENNY W. LEE, BAPPSC[3]
CHARLES F. VERGE, MBBS, PHD, FRACP[1,2]
KIM C. DONAGHUE, MBBS, PHD, FRACP[3,4]

OBJECTIVE — To describe the natural history and risk factors for persistent microalbuminuria in children and adolescents with type 1 diabetes followed for up to 15 years.

RESEARCH DESIGN AND METHODS — This study contained a longitudinal cohort of 972 patients; analysis of baseline risk factors was performed using logistic regression and predictors over time using survival analysis. Albumin excretion rate was measured on three consecutive timed overnight urine collections on at least two occasions. Normoalbuminuria was defined as a median albumin excretion rate <7.5 μg/min, borderline microalbuminuria as 7.5–20 μg/min, and microalbuminuria as 20–200 μg/min. Microalbuminuria was further classified as persistent if its duration was >12 months. Median age was 12.7 years (interquartile range 11.5–14.4) and diabetes duration 6.5 years (4.1–9.3) at first assessment, and median follow-up was 6.2 years (range 1–15.3).

RESULTS — The incidence of persistent microalbuminuria was 4.6 (95% CI 3.3–6.1) per 1,000 patient-years. Predictors of persistent microalbuminuria from the first assessment using multiple logistic regression were high cholesterol (odds ratio 2.2 [95% CI 1.2–4.0]) and borderline microalbuminuria (2.5 [1.2–5.2]). Predictors using Cox regression were HbA_{1c} (hazard ratio 1.4 [95% CI 1.1–1.7]), age at diagnosis (1.2 [1.1–1.3]), obesity (3.6 [0.8–15.5]), and insulin dose (2.7 [1.0–7.5]).

CONCLUSIONS — Children and adolescents with type 1 diabetes who have borderline microalbuminuria are more than twice as likely to develop persistent microalbuminuria. In addition to poor glycemic control, clinical markers of insulin resistance were associated with an increased risk of microalbuminuria.

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Microalbuminuria is well recognized as a risk factor for the development of diabetic nephropathy in adults, but its natural history is less clear in children and adolescents. Within 2 decades of diabetes onset, a single episode of microalbuminuria is found in 2–18% of children and adolescents with type 1 diabetes (1–3) but may be transient in up to half of cases (4,5). Established risk factors for microalbuminuria in adolescents and adults include duration of diabetes (5,6), suboptimal glycemic control (7,8), hypertension, and smoking (9).

Markers of insulin resistance have been associated with the development of microalbuminuria in adults with type 1 diabetes (10–14), although there is less evidence for this in children and adolescents. Of note, however, the incidence of microalbuminuria in type 1 diabetes increases at puberty (8), a time of exaggerated physiological insulin resistance (15–17). Indeed, higher androgens and growth hormone have been found in adolescents with type 1 diabetes in association with higher albumin excretion (18,19), while the effects of higher BMI and other features of the metabolic syndrome on the risk of microalbuminuria in this age-group are unclear.

The aims of this 15-year longitudinal study were to identify risk factors for early nephropathy and to explore the potential role of insulin resistance in the development of persistent microalbuminuria. We examined putative risk factors at initial assessment for the subsequent development of persistent microalbuminuria and used survival analysis to evaluate risk factors over time.

RESEARCH DESIGN AND METHODS

— Children and adolescents with type 1 diabetes attending complications assessment at The Children's Hospital at Westmead during 1989–2004 were included in this retrospective cohort study. Patients were screened according to established guidelines, which recommend annual assessment beginning 5 years after diagnosis in prepubertal children and 2 years after diagnosis in pubertal children (20,21). Complications assessment was undertaken during a 2-h visit that consisted of clinical assessment by the endocrinologist; anthropometry, blood pressure measurement, and pubertal staging; screening for retinopathy, microalbuminuria, and neuropathy; and HbA_{1c} (A1C) and biochemistry, as previously described (3). Patients were included in this study if albumin excretion rate (AER) had been measured two or more times, spaced at least 12 months

From the [1]Department of Endocrinology, Sydney Children's Hospital, Randwick, Sydney, Australia; the [2]School of Women's and Children's Health, The University of New South Wales, Sydney, Australia; the [3]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Westmead, Sydney, Australia; and the [4]Department of Paediatrics and Child Health, The University of Sydney, Sydney, Australia.

Address correspondence and reprint requests to Dr. Kim Donaghue, Paediatric Endocrinologist, Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Hawkesbury Road, Westmead, Sydney, Australia. E-mail: kimd@chw.edu.au.

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Abbreviations: AER, albumin excretion rate; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone–binding globulin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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apart. Complications assessment results from all visits were included in the analyses. Patients and their families gave informed consent for the results of the complications assessment to be analyzed. Approval was obtained by the Ethics Committee of the Children's Hospital at Westmead.

Three timed overnight urine specimens were collected immediately before the complications assessment. Urinary albumin was measured using a polyclonal radioimmunoassay (Pharmacia RIA, Beckman Coulter, Australia) from 1990 to March 2000. From April 2000, the laboratory changed to nephelometric assay using the IMMAGE analyzer (IMMAGE = [0.8734 × radioimmunoassay value] − 0.501, $r = 0.99$). Microalbuminuria was defined as an AER of 20–200 μg/min in at least two of three samples, and if present, repeat collections were requested 3 months later. Microalbuminuria was further classified as transient if it reverted to the normoalbuminuria range within 12 months and persistent if AER remained >20 μg/min for >12 months. Normoalbuminuria was defined as mean AER <7.5 μg/min in all urine samples collected. This cutoff approximates the 95th percentile for healthy children (22). Borderline microalbuminuria was defined as mean AER between 7.5 and 20 μg/min.

Retinopathy was assessed by seven-field fundal photography and graded according to the modified Airlie House Classification (23). Retinopathy was defined as at least one microaneurysm and one hemorrhage.

Height was measured using a Harpenden stadiometer (Holtain, Crymmych, U.K.) and weight using electronic scales. Obesity was defined as a BMI SD score ≥2 (24). Blood pressure was measured by auscultation after 5 min of rest, and percentiles were calculated based on age and sex (25).

At each complications assessment, glycemic control was assessed by glycated hemoglobin (GHb) calorimetrically (26) before February 1994 and subsequently by A1C using high-performance liquid chromatography (Diamat Bio-Rad; normal range 4–6%). GHb values were converted to A1C (Diamat = 1.9088 + 0.0043 × GHb, $r = 0.92$). The interassay coefficients of variation (CVs) were 1.1 and 1.2% for an A1C of 5.95 and 9.76%, respectively.

Biochemical markers of insulin resistance were assessed in a subgroup of 161 patients (73 males) with stored serum samples (24 with microalbuminuria and 137 with normoalbuminuria). IGF-I, sex hormone–binding globulin (SHBG), testosterone, and dehydroepiandrosterone sulfate (DHEAS) were measured using a solid-phase chemiluminescent immunometric assay (Immulite; DPC, Los Angeles, CA). Interassay CVs were 3.7% for IGF-I, 4.2% for SHBG, 6.5% for DHEAS, and 7.8% for testosterone.

Statistical analysis

Descriptive statistics are presented as mean (±SD) score for normally distributed data and median (interquartile range or range) for skewed data. DHEAS, IGF-I, SHBG, and free androgen index were compared in individuals with and without microalbuminuria by Mann-Whitney *U* tests.

Baseline risk factors

Early risk factors for the development of persistent microalbuminuria from the first ever complications assessment were examined using logistic regression. Patients who subsequently developed persistent microalbuminuria (defined as "case subjects") were compared with *1*) all other patients (labeled "others" in Table 1) and *2*) only those who continued to have normoalbuminuria (that is, patients with borderline microalbuminuria and transient microalbuminuria were excluded to avoid misclassification bias). Potential explanatory variables from the first ever complications assessment used in the regression models were BMI, blood pressure percentile, cholesterol, insulin dose, multiple injections (defined as three or more insulin injections per day), and A1C. Hypercholesterolemia was defined as a serum cholesterol >5.2 mmol/l (27). Clinically relevant interaction terms were examined; models were assessed for goodness of fit and compared using likelihood ratio tests.

Survival analysis

Cox proportional hazards regression analysis was used to account for differences in duration of follow-up. Duration of diabetes was used as the time varying coordinate, with development of persistent microalbuminuria as the outcome. The same explanatory variables were examined with all available time points included in the models. Statistical analysis was performed using Stata (version 8; StataCorp, College Station, TX).

RESULTS

— In the entire cohort ($n = 991$) at first assessment, median age was 12.7 years (interquartile range 11.5–14.4) and duration of diabetes was 6.5 years (4.1–9.3). The median duration of follow-up after the first complication assessment was 6.2 years (range 1.0–15.3), and the median number of assessments with AER measurements available was four per patient (range 2–12). Characteristics of patients with and without microalbuminuria are shown in Table 1.

Natural history

There was a progressive increase in AER in the years before the onset of persistent microalbuminuria (Fig. 1). At first assessment, microalbuminuria was found in 40 patients (4%) and borderline microalbuminuria in 184 (19%), and the remaining 767 had normoalbuminuria. Of those with normoalbuminuria at first assessment, 492 (64%) continued to have normoalbuminuria during follow-up, 212 (28%) had an episode of borderline microalbuminuria, and 59 (8%) had an episode of microalbuminuria. In total, 436 (44%) had an episode of borderline microalbuminuria at any time point; of these, 343 reverted to normoalbuminuria, 33 persisted as borderline microalbuminuria, and 60 progressed to microalbuminuria. Overall, 124 (12.4%) patients had an episode of microalbuminuria, 60 were transient, 45 were persistent, and 19 could not be classified because of insufficient follow-up information (and were excluded from further analysis, leaving 972 patients). None of the patients with transient microalbuminuria had been treated with ACE inhibitors.

The incidence of persistent microalbuminuria was 4.6 per 1,000 patient-years (95% CI 3.3–6.1). The median diabetes duration at the onset of persistent microalbuminuria was 9.3 years, and the earliest case was 1.6 years after diagnosis of diabetes. Six patients, all with preexisting microalbuminuria, developed macroalbuminuria. The median diabetes duration at the onset of macroalbuminuria was 11.5 years.

Baseline risk factors

Compared with all others, patients who subsequently developed persistent microalbuminuria were significantly more likely to have borderline microalbuminuria or microalbuminuria, hypercholesterolemia, blood pressure >95th percentile, obesity, and longer diabetes duration at the first complications assess-

Table 1—*Factors associated with persistent microalbuminuria in adolescents with type 1 diabetes: multiple logistic regression analysis using explanatory variables from the first ever complications assessment*

		Compared with all others			Compared with patients with normoalbuminuria		
At first complications assessment	Case subjects (n = 45)	All others (n = 929)	Univariate	Multivariate R^2 = 10%	Always normoalbuminuric (n = 492)	Univariate	Multivariate R^2 = 12.8%
Age (years)	13.7 ± 2.2	13.2 ± 2.2	1 (1.0–1.2)		15.4 ± 3.2	1.1 (1.0–1.2)*	
Duration (years)	6.7 ± 3.9	5.5 ± 3.1	1.1 (1.0–1.2)*		7.5 ± 3.7	1.1 (1.0–1.2)*	1.2 (1.0–1.3)†
Cholesterol ≥5.2 mmol/l	42.5%	21.5%	2.9 (1.5–5.5)†	2.2 (1.2–4.0)†	14.8%	2.5 (1.2–5.0)†	2.0 (0.7–5.5)
AER <7.5 μg/min (n)	19	695					
AER 7.5–20 μg/min (n)	13	188	2.5 (1.2–5.2)†	2.5 (1.2–5.2)†			
AER >20 μg/min (n)	15	48	11.4 (4.6–21.0)†	9.9 (4.6–21.0)†			
BMI SD score ≥2	24%	11%	2.5 (1.2–5.1)†		8.5%	8.5 (4.3–14.7)†	
≥3 injections	42.5%	37.7%	1.2 (0.6–2.3)		62.2%	1.4 (0.7–2.8)	
Blood pressure >95th percentile	35.5%	21.2%	1.9 (1.0–3.7)*		5.1%	3.6 (1.5–9.0)	3.0 (0.7–12.5)
A1C (%)	8.4 ± 1.2	8.6 ± 1.3	0.9 (0.7–1.1)		8.6 ± 1.5	1.3 (1.1–1.7)†	1.3 (1.0–1.7)*
Insulin dose (units · kg^{-1} · day^{-1})	1.2 ± 0.3	1.1 ± 0.3	1.5 (0.6–3.8)		1.2 ± 0.4	0.9 (0.3–2.7)	

Data are means ± SD or odds ratio (95% CI) unless otherwise indicated. Two different models were used: cases of persistent microalbuminuria were compared with *1*) the entire cohort (including patients with borderline microalbuminuria) and 2) patients with normoalbuminuria (AER <7.5 μg/min). The multivariate model included all explanatory variables except age (due to its colinearity with duration: correlation coefficient = 0.5) and interaction terms. *P < 0.01, †P < 0.05.

ment. In multivariate analysis, baseline borderline microalbuminuria, microalbuminuria, and hypercholesterolemia remained significant predictors of subsequent persistent microalbuminuria. When those with transient microalbuminuria or borderline microalbuminuria were excluded from the analysis, duration and glycemic control were the only significant variables in the multivariate model (Table 1).

Survival analysis

In Cox proportional hazards regression, higher A1C, older age at diagnosis, higher insulin dose, and obesity were predictive of the development of persistent microalbuminuria (Table 2).

Biochemical subanalysis

Patients with persistent microalbuminuria were older than patients with normoalbuminuria (17.4 vs. 16.0 years, respectively; P = 0.04) and their A1C was higher (9.1 vs. 8.3%, P = 0.02) but did not differ with regard to diabetes duration (10.2 vs. 10.3 years, P = 0.9) or BMI SD score (0.78 vs. 0.69, P = 0.7). DHEAS was significantly higher in patients with persistent microalbuminuria: 5.3 μmol/l (range 2.2–11.2) vs. 3.9 (0.4–15.8) (P = 0.02), and SHBG was significantly lower in females with persistent microalbuminuria (3.2 vs. 323.5 nmol/l, P = 0.03) but not males (35.0 vs. 52.1). There were no significant differences in serum IGF-I, testosterone, and free androgen index between the two groups overall and when stratified for sex.

CONCLUSIONS — In this longitudinal study of 972 youth with type 1 diabetes, the incidence of persistent microalbuminuria was 4.6 per 1,000 patient-years. Early elevation of AER at first complication assessment was a significant risk factor for the later development of persistent microalbuminuria, and there was a gradual rise in AER before the diagnosis. The modifiable risk factors identified for persistent microalbuminuria were hypercholesterolemia and glycemic control, in addition to the recognized risk factors of older age and duration. Markers of insulin resistance such as higher BMI, DHEAS, and higher insulin dose were also identified as predictors but did not remain significant in multivariate analysis, possibly because of our low rate of persistent microalbuminuria, despite the large cohort.

The main strengths of this study are

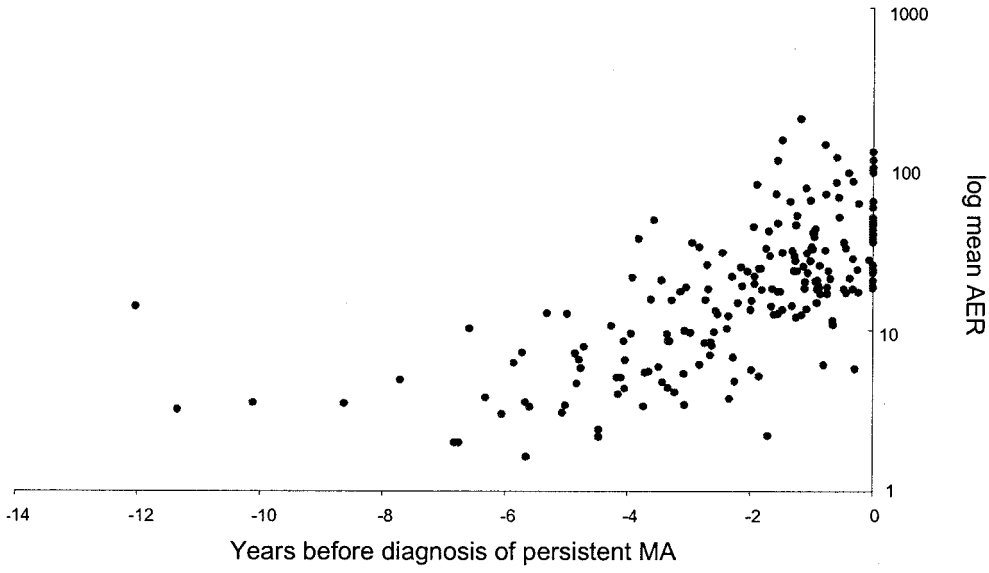

Figure 1—*Log mean AER in adolescents with type 1 diabetes at a single time point before the development of persistent microalbuminuria (MA). The natural history of AER before the development of persistent microalbuminuria is shown; the duration of diabetes before the onset of microalbuminuria is shown on the x-axis, and log mean AER at a single time point before the development of persistent microalbuminuria is shown on the y-axis. There is a negative correlation between log AER and time before development of microalbuminuria.*

its longitudinal nature and the number of patients followed over time. Although not population based, this cohort has similar characteristics to our previous population-based studies (28), and the long period of follow-up provides important information on natural history in a typical clinic population. Misclassification bias has been minimized by defining persistent microalbuminuria as being present on two occasions separated by at least 12 months. Despite the broad nature of the study population, there remains a possibility of sampling bias that may work to either inflate or deflate the reported incidence. Both patients more concerned about their health and risk of complications and patients with more risk factors for complications may be more likely to present for complication assessment. Although followed for up to 15 years, the study is underpowered because of the low incidence of persistent microalbuminuria. Sample size calculations indicate that more cases (at least 70) are needed to achieve adequate power for markers of insulin resistance that were significant in univariate analysis.

Borderline microalbuminuria at first complication assessment more than doubled the risk of persistent microalbuminuria compared with normoalbuminuria, and the effect persisted after adjusting for duration. This confirms previous studies in which early elevation of AER and the rate of rise of albumin-to-creatinine ratio within the normal range were predictors for microalbuminuria (8,29). While this could be explained by genetic predisposition to nephropathy (30–32), it argues for the possibility of intervention at a lower level of albuminuria than current guidelines recommended for adolescents (21).

Increasing age at diagnosis increased the risk of microalbuminuria in longitudinal analysis. Certainly, increasing duration of diabetes increases the risk of complications, but the use of survival analysis allowed age to be examined as an independent predictor of microalbuminuria. Although there are inconsistencies in the available literature in relation to the reported effects of prepubertal years of diabetes complications, often due to methodological differences (5,6,33), we have previously reported the risk for retinopathy and microalbuminuria increases as the child approaches the clinical onset of gonadarche (6). Furthermore, in the subgroup in which androgens were measured, DHEAS was higher in individuals with persistent microalbuminuria, who were also older.

Markers of insulin resistance, including hypercholesterolemia, adiposity as measured by BMI, higher insulin dose, and higher androgens, were associated with the development of persistent microalbuminuria. Insulin resistance without diabetes has been linked to microalbuminuria in adults (34), and elevation of AER may begin in childhood in association with obesity and other features of the metabolic syndrome (35). This is particularly relevant considering the epidemic of obesity seen among children and adolescents in developed countries (36,37), and those with type 1 diabetes are not immune (38). In addition, insulin omission in type 1 diabetes

Table 2—***Longitudinal analysis of factors associated with persistent microalbuminuria in adolescents with type 1 diabetes: results of the Cox proportional hazards regression using all available data points***

	Univariate analysis		Multivariate model*	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age at diagnosis	1.2 (1.1–1.3)	<0.01	1.2 (1.1–1.3)	<0.01
A1C	1.4 (1.1–1.7)	<0.01	1.4 (1.1–1.7)	0.01
Blood pressure >95th percentile	2.8 (1.1–7.2)	0.03		
Cholesterol ≥5.2 mmol/l	1.9 (1.1–3.6)	0.03		
BMI SD score ≥2	2.1 (1.1–3.8)	0.02	3.6 (0.8–15.5)	0.09
Insulin dose	2.3 (0.9–6.3)	0.1	2.7 (1.0–7.5)	0.06
≥3 injections	1.3 (0.7–2.5)	0.4		

*The multivariate model adjusts for all explanatory variables listed in the table and interaction terms; the model of best fit includes independent predictors of persistent microalbuminuria ($P < 0.1$). All patients were included in this model.

can cause the same clinical features as seen in insulin resistance, that is, high reported insulin requirement, elevated cholesterol, triglycerides and free fatty acids, and hepatic steatosis. Furthermore, there are interactive relationships between insulin dose, glycemic control, and BMI SD score. Although insulin dose is a marker of insulin resistance (39,40), it also varies with carbohydrate consumption, physical activity (which we did not measure), insulin type, and regimen and can be misreported, particularly in noncompliant adolescents.

This study indicates that individuals with borderline microalbuminuria need to be followed closely, since they are at increased risk of developing microalbuminuria. The transient nature of microalbuminuria in children and adolescents would suggest the need for at least 12 months of documented microalbuminuria before treatment is considered. Identifying young people most at risk of nephropathy is important to allow timely and appropriate intervention. There is good evidence in adults that ACE inhibitors and angiotensin II blockers are useful in the prevention of diabetic nephropathy (41), as is optimizing glycemic control. Our study also suggests preventative strategies should address insulin resistance in young people with type 1 diabetes.

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