Determinants of Progression of Microalbuminuria in Adolescents With IDDM

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OBJECTIVE — To evaluate the significance of microalbuminuria in adolescents with IDDM and to study the relative importance of blood pressure (BP), metabolic control, and albumin excretion rate (AER) on progression of microalbuminuria.

RESEARCH DESIGN AND METHODS — A cohort of 155/156 children and adolescents followed from onset up to 18.3 years of IDDM participated. In a previous follow-up in July 1991 (up to 15 years of duration), 17 patients had developed persistent microalbuminuria (≥20 μg/min). In these adolescents, we analyzed whether microalbuminuria had progressed (in mean ≥5% per year), had remained unchanged, or had normalized (<20 μg/min) after another 3 years. The predictive values of mean HbA_{1c}, diastolic blood pressure (dBP), systolic blood pressure (sBP), overnight AER, sex, age, and duration of diabetes for the progression of microalbuminuria were determined using multiple regression modeling.

RESULTS — Seven of 17 patients with microalbuminuria in July 1991 had normalized, 6 of 17 patients had progressed, and 4 of 17 patients had remained unchanged after 3 years. Progressors had higher mean HbA_{1c} during the first 5 years of IDDM and higher mean sBP in 1991 than nonprogressors. Patients with normalized microalbuminuria all had AER <30 μg/min in 1991, were younger at onset of microalbuminuria, had lower mean HbA_{1c}, and had lower dBP before normalized AER than nonregressors at the same duration of microalbuminuria. In multivariate analysis, independent significant predictors for progression were first 5-year mean HbA_{1c}, mean AER, and mean sBP in 1991 ($R^2 = 0.76$, $P = 0.001$).

CONCLUSIONS — Progression of microalbuminuria in adolescents with IDDM is predicted by early sustained hyperglycemia, later elevated sBP, and increased AER per se. Microalbuminuria is frequently normalized in adolescents, and this is associated with better prevailing metabolic control, younger age, and lower dBP.

Onset of IDDM before 20 years of age confers an increased risk for diabetic nephropathy (1), and puberty seems to play a central role in the initiation of microalbuminuria (2,3). Persistent microalbuminuria >20 μg/min predicts diabetic nephropathy with high specificity but less sensitivity in adults (4–6), but the prognostic implications of microalbuminuria in adolescents is unsettled.

Factors predicting onset of microalbuminuria (3,7,8) may partly differ from those promoting the progression. We have reported earlier the cumulative incidence of microalbuminuria (>20 μg/min) to be 24% up to 15 years of duration in IDDM adolescents (3). We also found a fourfold increased risk for onset of microalbuminuria when having a mean HbA_{1c} >7.5% during the first 5 years of diabetes. Blood pressure (BP) was normal before onset of microalbuminuria and was no risk factor for the onset (3). In the present study, we followed this cohort for another 3 years to evaluate *1*) the cumulative incidence of microalbuminuria up to 18.3 years of IDDM and 2) the relative importance of glycemic control (early and present), BP, albumin excretion rate (AER), age at onset of microalbuminuria, and IDDM duration on the progression of microalbuminuria.

RESEARCH DESIGN AND METHODS

Of the cohort of 156 patients followed from onset of IDDM (4), 155 (67 boys, 88 girls) participated in the final follow-up in 1994. One girl had moved. Diabetes duration (mean ± SE) was 9.8 ± 0.3 years, mean age 17.0 ± 0.3 years. In a previous follow-up in 1991, 17 patients had developed persistent microalbuminuria, defined as AER 20–200 μg/min in at least two of three consecutive overnight urine samples (9). After 1991, five subjects (one with microalbuminuria) received insulin pump treatment and other subjects received multiple injection therapy. Four subjects (three with microalbuminuria) received ACE inhibitors (enalapril 20 mg/day) because they had systolic blood pressure (sBP) and/or diastolic blood pressure (dBP) levels ≥140/90 mmHg. The BP levels in those with microalbuminuria were 148/80, 140/95, and 130/90 mmHg, respectively, at the time for prescription in 1992. A low-protein diet was not used.

HbA_{1c}, BP, and AER were analyzed two to four times yearly by the same methods as in the previous follow-up (3). HbA_{1c} was analyzed by high-performance liquid chromatography (reference level 4–6%), and BP was analyzed by an automatic device (3). Timed overnight AER was analyzed on fresh urine by immunoturbidimetry (Instrumentation Lab, Lexington, MA). Intra-assay coefficient of variation was 3%, and interassay coefficient of variation was 4.7% in the range 10–50 mg/l.

The cumulative incidence of microalbuminuria was estimated by the Kaplan-Meier life-table method (10). Pro-

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AER, albumin excretion rate; BP, blood pressure; dBP, diastolic blood pressure; sBP, systolic blood pressure.

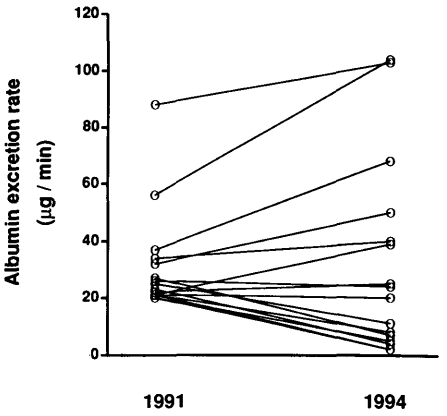

Figure 1—*Changes in AER between 1991 and 1994 in 17 patients with persistent microalbuminuria ≥20 μg/min in 1991.*

Table 1—*Clinical data on patients with persistent microalbuminuria >20 μg/min in 1991 who had progressed or had unchanged or normalized AER within 3 years of follow-up*

	Progressed	Unchanged	Normalized
n	6	4	7
Sex (M/F)	4/2	0/4	2/5
Duration of diabetes in 1991 (years)	10.5 ± 1.8*	9.5 ± 1.7	7.8 ± 0.9
Duration of microalbuminuria in 1991 (years)	2.0 ± 0.5	1.5 ± 0.8	1.8 ± 0.5
Age at onset of microalbuminuria (years)	15.6 ± 1.5*	14.9 ± 1.6	13.0 ± 1.1
First 5-year mean HbA_{1c} (%)	8.9 ± 0.6*‡	7.4 ± 0.8	7.1 ± 0.3
Mean HbA_{1c} 1991 (%)	9.4 ± 1.2*	9.2 ± 1.8*	7.2 ± 0.2
Mean HbA_{1c} 1991–1994 (%)	8.7 ± 1.0	8.9 ± 1.1	7.9 ± 0.4
Mean sBP 1991 (mmHg)	140 ± 4†§	123 ± 3	125 ± 3
Mean dBP 1991 (mmHg)	81 ± 5	78 ± 2	70 ± 1
Mean sBP 1991–1994 (mmHg)	135 ± 4*‡	122 ± 2	126 ± 2
Mean dBP 1991–1994 (mmHg)	79 ± 3*	79 ± 2*	71 ± 2

Data are means ± SE. *$P < 0.05$; †$P < 0.01$ vs. normalized; ‡$P < 0.05$; §$P < 0.01$ vs. unchanged.

gression of microalbuminuria was defined as a yearly mean increase in AER ≥5% based on more than two measurements per year, and normalized microalbuminuria was defined as AER persistently <20 μg/min based on more than two consecutive samples in 1994. Comparisons between groups were performed by one-way analysis of variance and single correlations by the Pearson method. Stepwise multiple regression analysis was applied to identify independent significant predictors of increase in AER in patients with microalbuminuria in 1991. AER was log-transformed before calculations.

RESULTS — Seven of 17 patients with microalbuminuria in 1991 were normoalbuminuric in 1994. They all had a mean AER <30 μg/min in 1991. Of the 17 patients, 4 had unchanged AERs (<5% increase per year) and 6 had progressed (Fig. 1). Since 1991, another four patients had developed persistent microalbuminuria >20 μg/min, two of these >30 μg/min. The cumulative incidence by duration of microalbuminuria >20 μg/min was 14.6% up to 18.3 years of IDDM. Using >30 μg/min as the risk level, the cumulative incidence was 11.9%.

Patients with onset of microalbuminuria before 12 years of age and/or before 5 years of IDDM ($n = 6$) were normoalbuminuric in 1994. Diabetes duration and age at onset of microalbuminuria were higher in progressors than in subjects with normalized AER. First 5-year mean HbA_{1c} and mean sBP in 1991 and between 1991–1994 was higher in progressors than in the other groups. Mean HbA_{1c} in 1991 and dBP between 1991 and 1994 was lower in patients with normalized AER than in the other groups (Table 1).

Variables that significantly ($P < 0.05$) correlated with the increase in AER were AER in 1991 ($r = 0.60$), sBP in 1991 ($r = 0.60$), and first 5-year mean HbA_{1c} ($r = 0.58$). In the stepwise multiple regression, only first 5-year mean HbA_{1c}, AER, and sBP in 1991 had an independent significant influence on the increase in AER 3 years later, whereas duration of IDDM, age at onset of microalbuminuria, sex, mean HbA_{1c}, and mean dBP in 1991 had not and were not included in the final equation (Table 2).

CONCLUSIONS — The cumulative incidence of diabetic nephropathy in childhood-onset IDDM was reported to have decreased to ~10% in one region of Sweden (11). This agrees with the cumulative incidence of microalbuminuria >30 μg/min of ~12% in our study. Only 35% of the adolescents with persistent microalbuminuria >20 μg/min progressed during this 3-year follow-up study. Using a comparable at-risk level in IDDM adults, it was earlier reported that 40–46% progressed in microalbuminuria during 2–7 years (6,12,13). However, with overnight AER >30 μg/min as exposure level, we found the predictive value for progression of microalbuminuria to be 100%. AER >30 μg/min was earlier classified as the at-risk level in overnight urine (14) with 87.5% developing diabetic nephropathy after 23 years (15). This cut-off level of overnight AER may thus be a more reliable risk marker for nephropathy.

We earlier reported the relative importance of high mean HbA_{1c} during the first 5 years of IDDM in the occurrence of microalbuminuria (3). We here confirm that early hyperglycemia is also a predictor for progression when age at onset of microalbuminuria, duration of IDDM, BP, and prevailing HbA_{1c} are accounted for.

It has been proposed that albuminuria per se may enhance the advancement of glomerulopathy (16). This hypothesis is compatible with our finding that the degree of microalbuminuria is an independent risk determinant for progression. Elevated BP is no prerequisite for onset of microalbuminuria (3,8,12). However, once AER has increased, hypertension accelerates diabetic nephropathy.

Table 2—*Stepwise multiple regression results with the increase in log AER between 1991–1994 as the dependent variable in 17 patients with microalbuminuria in 1991*

Independent variables	R^2	*F* value	*P* value
Log AER, 1991	0.47	13.3	0.003
Log AER, 1991; first 5-year mean HbA_{1c}	0.74	18.7	<0.001
Log AER, 1991; first 5-year mean HbA_{1c}; sBP, 1991	0.76	20.0	<0.001

In accordance, we found that elevated sBP was also a predictor for progression of microalbuminuria when the possible confounding of age was accounted for. Microalbuminuria is reduced in normotensive IDDM patients after treatment with ACE inhibitors (5,17). One of our patients with unchanged microalbuminuria (<5% per year) and two with a slow progression rate (~5% per year), but none of our patients with normalized microalbuminuria, had been taking enalapril for 2 years. This reduced their mean BPs between 5 and 10%. It is possible that ACE inhibition may have retarded the progression rate of microalbuminuria, but with the limited number of patients such an effect cannot be assessed.

We did not study several potential risk factors for diabetic nephropathy. Still, 76% of the variation of progression was explained by early metabolic control preceding AER and sBP levels. The high regression frequency (41%) of persistent low-grade microalbuminuria is noteworthy and seems higher than in adults by ~10% (5). The possibility that normalized microalbuminuria occurred as a result of an initial misclassification of a patient due to high day-to-day variability is unlikely because all patients who became normoalbuminuric had persistent microalbuminuria >1 year before regression. Patients with normalized AER had lower preceding HbA_{1c} and dBP than progressors. Improved glycemic control may reverse microalbuminuria (18,19). A dBP in the lower normal range was recorded in IDDM patients with long-time survival (20). Thus, in the long run, a maintained normalized AER may depend on continuously good metabolic control and normal dBP.

In summary, progressive microalbuminuria with onset in pubertal ages is predisposed by early hyperglycemia and enhanced by high sBP and elevated AER itself. Low-grade microalbuminuria is frequently normalized in IDDM adolescents and related to a good prevailing metabolic control and a dBP within the lower normal range. Prepubertal age and short diabetes duration seem invariably associated with reversed microalbuminuria.

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