Enhanced Progression of Urinary Albumin Excretion in IDDM During Puberty

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OBJECTIVE — To determine whether the progression of urinary albumin excretion rate (AER) is higher during puberty than before or after this period.

RESEARCH DESIGN AND METHODS — A prospective study was conducted in which normoalbuminuric prepubertal (n = 20), pubertal (n = 28), and postpubertal (n = 26) IDDM groups matched for diabetes duration and long-term metabolic control were followed for 3 years. At 6-month intervals, 24-h urine collection was used to determine AER.

RESULTS — AER increased significantly over a period of 3 years in the pubertal (P = 0.001) and postpubertal (P = 0.003) subjects but not in prepubertal subjects. The annual progression of AER was significantly higher in the pubertal group than in the prepubertal (P = 0.001) or postpubertal (P = 0.001) groups. Six pubertal, two postpubertal, and none of the prepubertal subjects developed microalbuminuria (AER ≥20 μg/min on two consecutive occasions) over a 3-year period (P = 0.047). Multiple logistic regression analysis showed that the risk of development of microalbuminuria was increased in pubertal subjects compared with the prepubertal and postpubertal subjects (adjusted relative risk [95% CI]: 4.3 [1.5–9.3], P = 0.012, and 2.1 [1.1–5.0], P = 0.023, respectively).

CONCLUSIONS — Puberty represents an independent risk of the development of microalbuminuria in diabetes. This finding suggests that the endocrine changes of puberty lead to an accelerated process of early kidney damage in diabetes. In pediatric diabetes care, screening for microalbuminuria is needed soon after the onset of puberty.

Diabetic nephropathy, a major cause of death in diabetes, develops in as many as 30–50% of individuals with IDDM (1,2). Persistent microalbuminuria is rare in children and adolescents (3–5); however, patients with childhood-onset IDDM are considered to be particularly at risk of diabetic nephropathy (6).

It is well documented that persistent microalbuminuria is a strong predictor of overt nephropathy (7–10) and that the development of microalbuminuria is associated with progressing glomerular structural changes (11). Although the pathogenesis of kidney damage in diabetes is not well understood, significant contributors to the risk of developing nephropathy include diabetes duration, long-term metabolic control, and genetic susceptibility (12–14). Furthermore, retrospective and cross-sectional studies found a relationship between the occurrence of microalbuminuria and the pubertal period and suggested that puberty may play a critical role in the development of diabetic nephropathy (3–5,15–19). To our knowledge, only one study prospectively examined the influence of puberty on the occurrence of persistent microalbuminuria in diabetic children and adolescents, although it failed to control for duration of diabetes (20).

Therefore, the aim of our present study was to assess the influence of pubertal development on the urinary albumin excretion rate (AER) prospectively in peripubertal diabetic children and adolescents. With this purpose, prepubertal, pubertal, and postpubertal groups of patients with similar disease duration were followed for 3 years, and the progressions of AER over time were compared.

RESEARCH DESIGN AND METHODS

Study design

Out of nearly 200 patients attending our diabetes outpatient clinic, a total of 80 children and adolescents with IDDM were considered for participation in this prospective study. Patients fulfilled the following inclusion criteria: *1*) age ≥6 years, 2) duration of diabetes ≥2 years, 3) normoalbuminuria (AER <20 μg/min on two consecutive occasions 2–4 weeks apart), 4) no clinical evidence of diabetes complications, 5) absence of chronic disease other than diabetes, 6) normal blood pressure for age and sex by clinical measurements. Patients were followed for 3 years and were assigned to one of three groups on the basis of pubertal stages defined according to Tanner criteria (T1–5): prepubertal (T1 at both entry and exit), pubertal (T2 at entry and T3–4 at exit), and postpubertal (T5). During the follow-up period, two prepubertal patients entered puberty and four pubertal patients progressed to postpubertal stage; these patients were excluded from later analysis. The three groups were carefully matched for diabetes duration and long-term metabolic control (Table 1). All patients were treated with combinations of short- and intermediate-acting human insulin injected two to five times daily. The majority of patients, especially those who were pubertal and postpubertal, were treated using a regimen of multiple insulin injections. All parents and children were encouraged by the diabetes care team to achieve optimal metabolic control. Subjects and their parents gave their informed consent, and the study was approved by the regional ethics committee.

Assessments

Patients underwent formal physical exami-

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Abbreviations: AER, albumin excretion rate; GH, growth hormone; RR, relative risk; SDS, standard deviation score.

Table 1—*Characteristics of IDDM patients*

	Prepubertal	Pubertal	Postpubertal	*P* value
n (M/F)	20 (10/10)	28 (15/13)	26 (13/13)	—
Age at entry (years)	7.5 ± 1.2	11.6 ± 0.5	15.2 ± 0.7	0.0001
Diabetes duration at entry (years)	3.0 ± 0.4	3.2 ± 0.6	3.1 ± 0.5	0.42
BMI (SDS)				
At entry	−0.02 ± 0.5	0.11 ± 0.7	0.08 ± 0.3	0.70
At exit	−0.05 ± 0.4	0.09 ± 0.5	0.08 ± 0.4	0.50
Height (SDS)				
At entry	0.13 ± 0.7	0.05 ± 0.4	0.09 ± 0.5	0.87
At exit	0.09 ± 0.5	0.06 ± 0.3	0.10 ± 0.4	0.93
Body surface area (m^2)				
At entry	0.83 ± 0.18	1.22 ± 0.21	1.53 ± 0.20	0.0001
At exit	1.11 ± 0.20	1.53 ± 0.22	1.72 ± 0.23	0.0001
Average HbA_{1c} since diagnosis (%)				
At entry	7.8 ± 0.8	8.2 ± 1.1	8.0 ± 0.7	0.32
At exit	8.0 ± 0.6	8.4 ± 0.9	8.1 ± 0.8	0.19
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)				
At entry	0.7 ± 0.2	0.8 ± 0.3	0.9 ± 0.2	0.03
At exit	0.8 ± 0.3	1.0 ± 0.2	0.9 ± 0.3	0.04
Systolic blood pressure (SDS)				
At entry	0.10 ± 0.3	0.08 ± 0.4	0.12 ± 0.5	0.94
At exit	0.07 ± 0.4	0.09 ± 0.3	0.10 ± 0.4	0.96
Diastolic blood pressure (SDS)				
At entry	0.06 ± 0.6	0.03 ± 0.3	0.09 ± 0.5	0.90
At exit	0.10 ± 0.5	0.02 ± 0.3	0.07 ± 0.4	0.78
Cholesterol (mmol/l)				
At entry	4.0 ± 0.5	3.9 ± 0.4	4.1 ± 0.5	0.29
At exit	3.8 ± 0.6	4.0 ± 0.5	3.9 ± 0.5	0.43
Triglycerides (mmol/l)				
At entry	0.9 ± 0.1	0.9 ± 0.2	1.0 ± 0.2	0.08
At exit	1.0 ± 0.3	1.1 ± 0.4	1.1 ± 0.3	0.54

Data are means ± SD.

nation during follow-up visits to the clinic at 2- to 3-month intervals. Pubertal development was assessed according to Tanner criteria (breast and pubic hair stages for girls; genitalia and pubic hair stages for boys) rating in five stages (T1–5) (21). Blood pressure was measured at 6-month intervals using a sphygmomanometer with the subject in the seated position. BMI (kg/m^2) was used to estimate body composition. Blood pressure, BMI, and height were expressed as standard deviation scores (SDS). SDSs were calculated according to the formula $(X_i - M_x)/S_x$, where X_i is the actual measurement, M_x is the mean value for that age and sex, and S_x is the standard deviation corresponding to that age and sex.

To assess AER, 24-h urine collections were obtained. Patients were instructed to avoid vigorous exercise during the collections. The AER at the entry of the study was calculated from the mean of two consecutive collections 2–4 weeks apart. During follow-up, AER was determined every 6 months over a period of 3 years, and each mean of two consecutive values (at 1, 2, and 3 years) was used for analysis. Mean annual progression of AER was calculated for each patient. Microalbuminuria was defined as AER ≥20 μg/min on two consecutive measurements. Repeated urine samples obtained at baseline were used to assess the reliability of AER. The coefficient of reliability [1 − (within-person variance of the difference between repeated measurements/between-person variance of a single measurement)] was high (0.96) in this study. Adequacy of the 24-h collections was assessed by measurement of urinary creatinine excretion (normal range, 80–265 μmol $\cdot l^{-1} \cdot kg^{-1} \cdot day^{-1}$). Long-term metabolic control was estimated by the average HbA_{1c} since diagnosis, measured at 3-month intervals. Cholesterol and triglycerides were determined at yearly intervals.

After exclusion of proteinuria due to urinary tract infection, urinary albumin concentration was measured by an immunonephelometric method (Turbox Microalbuminuria Assay; Orion Diagnostica, Espoo, Finland) with intra- and interassay coefficients of variation of 3 and 5%, respectively. HbA_{1c} was measured by an ion-capture assay (IMx Glycated Hemoglobin Assay; Abbott, Chicago), with a nondiabetic range of 4.4–6.4%. Routine laboratory methods were used to measure cholesterol and triglyceride levels.

Statistical analysis

Clinical characteristics of study groups are given as means ± SD, and AERs are expressed as median and associated interquartile ranges. Distribution was tested for each variable by the Kolmogorov-Smirnov test. Variables having skewed distribution were transformed to natural logarithm before further analysis. For comparisons among groups and for repeated measures within groups, one-way analysis of variance was performed. Where overall significance was attained, differences between any two groups were tested by the Mann-Whitney rank-sum test or Wilcoxon's test. Fisher's exact test was used to assess association between categorical variables. Multiple logistic regression analysis was applied for discrete binary variables, and relative risks (RRs) with 95% CIs were calculated. *P* values < 0.05 were considered statistically significant.

RESULTS — Changes in AER over time in the study groups are shown in Fig. 1. Statistically significant increase in AER was observed in the pubertal diabetic group (baseline, 4.9 [2.8–7.6]; 1st year, 9.8 [7.1–14.8]; 2nd year, 12.1 [9.2–17.5]; 3rd year, 14.8 [12.0–18.6] μg/min; $P = 0.001$) and the postpubertal diabetic group (baseline, 4.6 [2.6–7.7]; 1st year, 7.0 [4.5–10.2]; 2nd year, 8.3 [5.6–12.0]; 3rd year, 8.5 [6.2–12.3] μg/min; $P = 0.003$) during the study period. In the prepubertal group, no significant change in AER was detected over the 3-year period (baseline, 4.8 [2.5–8.1]; 1st year, 4.7 [2.3–8.5]; 2nd year, 5.2 [2.6–8.6]; 3rd year, 5.1 [2.7–8.9] μg/min; $P = 0.866$). Average HbA_{1c}, lipid parameters, and blood pressure did not differ in the three groups. Insulin dose increased significantly from prepuberty to postpuberty (Table 1). The calculated annual progression rate of AER was significantly higher in the pubertal group com-

pared with the prepubertal and postpubertal groups (3.30 [3.07–3.67] vs. 0.10 [0.07–0.27] μg · min^{-1} · year^{-1}, $P = 0.001$, and 1.30 [1.20–1.53] μg · min^{-1} · year^{-1}, $P = 0.001$, respectively) (Fig. 2). Six patients (four girls and two boys with diabetes duration of 3–6 years) in the pubertal group developed microalbuminuria over the 3-year follow-up, compared with two patients (one girl and one boy with diabetes duration of 4 and 5 years, respectively) in the postpubertal group and no patients in the prepubertal group ($P = 0.047$). To assess which factors were associated with the development of microalbuminuria, multiple logistic regression analysis was performed on the combined cohort of diabetic patients using the presence of microalbuminuria as the dependent variable. The initial model included gender, puberty, duration of diabetes, BMI, height, body surface area, long-term metabolic control, daily insulin dose, systolic and diastolic blood pressure, and cholesterol and triglyceride levels as independent variables. Puberty, long-term metabolic control, diabetes duration, and body surface area remained in a model that was highly predictive of microalbuminuria ($P = 0.001$). In this multivariate analysis, puberty represented an independent risk of the development of microalbuminuria as compared with the prepubertal and postpubertal periods (adjusted RR [95% CI]: 4.3 [1.5–9.3], $P = 0.012$, and 2.1 [1.1–5.0], $P = 0.023$, respectively).

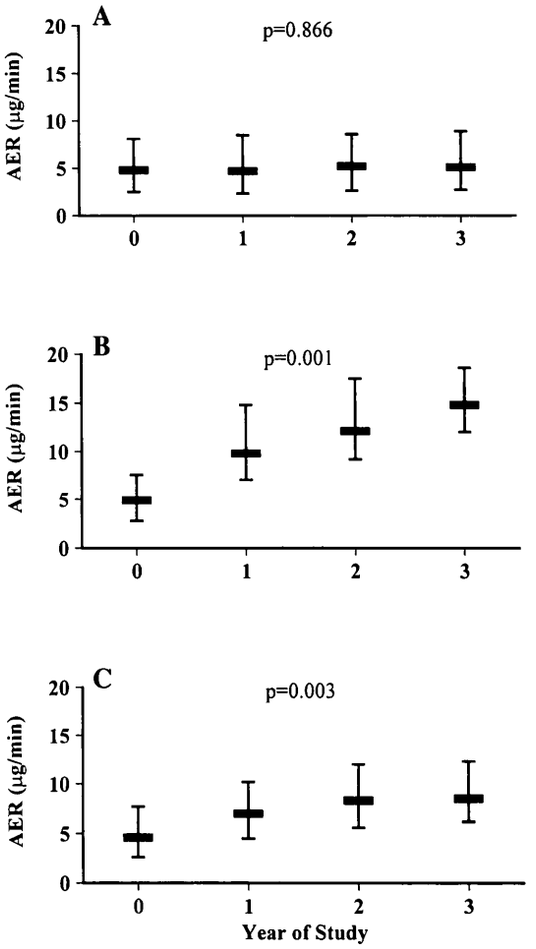

Figure 1—*AER during follow-up in prepubertal* (A), *pubertal* (B), *and postpubertal* (C) *groups. Values are expressed as medians (interquartile ranges).*

CONCLUSIONS — In this 3-year prospective study, a steady increase in AER was observed in the pubertal and postpubertal IDDM patients. By contrast, AER in prepubertal patients did not change over time. The highest progression rate of AER was recorded in the pubertal group, and the puberty proved to be a significant and independent risk factor for the development of microalbuminuria.

Epidemiological data have indicated that the pubertal and postpubertal years of diabetes mainly contribute to the risk of development of diabetic nephropathy (2,15). Other studies have indicated that persistent microalbuminuria rarely occurs in the prepubertal child but increases significantly after the onset of puberty (4,5,16,17). These observations suggest that puberty may initiate or accelerate the development of diabetic nephropathy, although exact pubertal staging to describe maturation was not applied in these studies. In a

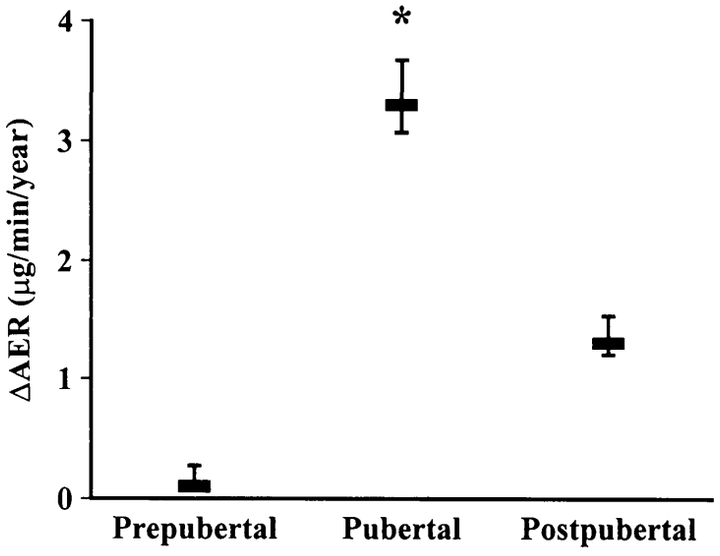

Figure 2—*Annual progression of AER (Δ AER) in patient groups studied. Values are expressed as medians (interquartile ranges).* *P = *0.001 vs. prepubertal and postpubertal groups, respectively.*

recent cross-sectional study by Mortensen et al. (18), AER increased with age in both diabetic and healthy children; however, after the onset of puberty (T2), this relationship was observed in diabetic subjects, but not in healthy subjects. In an 8-year prospective longitudinal study of 164 diabetic children and adolescents, Janner et al. (20) investigated the occurrence of microalbuminuria in relation to pubertal stages. They observed that approximately two-thirds of their subjects became microalbuminuric in the early to middle stages of puberty and that only one-third developed microalbuminuria after this period. However, neither this prospective study nor the previous cross-sectional studies controlled for duration of diabetes. More recently, Lawson et al. (19) investigated cross-sectionally prepubertal, pubertal, and postpubertal patients with similar diabetes duration and found that increased kidney volume and the prevalence of microalbuminuria were associated with increased pubertal duration. Our present prospective study provides evidence of the detrimental effect of the pubertal period on the progression of albuminuria, which is independent of the metabolic control or diabetes duration, and supports the concept that the pubertal milieu leads to an accelerated process of diabetic kidney damage.

The mechanism by which puberty enhances the progression of glomerular damage is not known. It has been the common experience that puberty is accompanied by increased insulin requirements, and that in a given patient, levels of glycemia are higher and fluctuate more during puberty than before puberty (22). It is generally accepted that hyperglycemia is a major contributing factor to the development of the microvascular complications of IDDM (12). Relative insulin resistance has been also suggested as a positive predictive factor (23), but in the present study, insulin doses were not associated with microalbuminuria. In accordance with previous suggestions (24), our data demonstrate that hyperglycemia occurring before puberty does not lead to as much microvascular damage as the same degree of hyperglycemia occurring during or after puberty. This finding suggests that additional factors contributing to kidney damage exist during puberty. Experimental data suggest that hormonal and metabolic changes during puberty could modify the development of nephropathy. Sex steroids, which rise dramatically during puberty, have been shown to exert an effect on potential pathogenic mechanisms in experimental diabetic nephropathy such as the polyol pathway and collagen cross-linking (25,26). Another association with puberty is a rise in levels of growth hormone (GH) and IGF-I, which has been implicated in the genesis of diabetic nephropathy (27–30). To date, the association of serum IGF-I levels and microalbuminuria in diabetic patients is unclear. IGF-I was found to be increased in adult patients with overt proteinuria (31) and decreased in children and adolescents with microalbuminuria (32). Nevertheless, it has been shown that pubertal diabetic patients exhibit disproportionately elevated GH and low IGF-I levels, indicating some kind of GH resistance (33,34). It could be speculated that oversecretion of GH may contribute to the early kidney damage, as suggested by animal studies (35).

In conclusion, more pronounced progression of albuminuria in IDDM patients occurs during puberty than before or after this period. Persistent microalbuminuria may develop in a pubertal child as early as 3 years after the onset of diabetes, supporting the concept that the endocrine or metabolic changes of puberty can lead to an early initiation or acceleration of kidney damage, although further studies are necessary to clarify the pathomechanism. In pediatric diabetes care, screening for microalbuminuria should be performed soon after the onset of puberty, and efforts should be made to maintain as near normal glycemic levels as is feasible.

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