The Effect of Prepubertal Diabetes Duration on Diabetes

Microvascular complications in early and late adolescence

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OBJECTIVE — To define the significance of prepubertal diabetes duration in the development of diabetic microvascular complications in adolescents.

RESEARCH DESIGN AND METHODS — Study A compares complications in 38 prepubertal (PreP) and 140 pubertal (Pub) subjects of the same age (10–14 years) and diabetes duration (3–12 years) to determine if the absence of puberty itself confers a lower risk of complications. Study B examines the importance of prepubertal and pubertal diabetes duration in 193 older adolescents (ages 15–22 years) with prepubertal onset of diabetes. Retinopathy status was assessed using stereoscopic fundus photography of seven fields per eye. Albumin excretion rate (AER) was assessed by three consecutive overnight urine collections, using a polyclonal radioimmunoassay.

RESULTS — In study A, there were no significant differences between the PreP and Pub groups for retinopathy (27 vs. 29%, $P = 0.8$) or differences in elevated AER (17 vs. 31%, $P = 0.1$). In study B, longer prepubertal diabetes duration improved the prediction for retinopathy over postpubertal duration alone ($P < 0.0005$). No relationship with duration was found for elevated AER (>7.5, >15, and >30 μg/min).

CONCLUSIONS — Prepubertal subjects with diabetes did not have less retinopathy or elevated albumin excretion compared with pubertal subjects of the same age. Prepubertal diabetes duration is significantly related to the presence of retinopathy in adolescents.

The hormonal changes of puberty have been perceived as playing a permissive role in the damaging effects of diabetes on the microvasculature. The contribution of prepubertal diabetes duration has been considered minimal compared with the effect of postpubertal duration in adolescents and adults (1). However, prepubertal diabetes duration has been significantly associated with the development of complications in recent studies of adolescents (2) and adults (3).

Early retinopathy and microalbuminuria have been documented in the prepubertal child (4,5). Cross-sectional studies have shown lower rates of microvascular complications in younger patients compared with older adolescents and young adults (4,6) but have included young children with shorter diabetes duration (4).

In an effort to define the significance of prepubertal diabetes duration in the development of diabetes microvascular complications during adolescence, this study comprises two cross-sectional analyses from our diabetes complications screening program. Study A compares complications in prepubertal and pubertal adolescents (ages 10–14 years) to determine if the absence of puberty itself confers a lower risk of complications. Study B examines the importance of prepubertal and pubertal diabetes duration in older adolescents with prepubertal onset of diabetes.

RESEARCH DESIGN AND METHODS

— All patients in our diabetes clinics are recommended to have diabetes complications screening from age 11 years with diabetes duration >3 years. Some patients are screened earlier if requested by their families or doctor. Patients and their parents give informed consent for the results to be analyzed (as approved by the Royal Alexandra Hospital for Children Ethics Committee).

Study A

This is an analysis of retinopathy and albumin excretion rate (AER) in young adolescents in whom abnormalities are compared in relation to gonadarche. Of 234 patients ages 10–14 years screened from January 1990 to December 1994, 38 were prepubertal (PreP). These patients were compared with 140 pubertal (Pub) patients with the same diabetes duration range (Table 1).

Study B

This is an analysis of complications in 193 older adolescents (ages 15–22 years) with prepubertal onset of diabetes. From a total of 256 adolescents assessed, 63 were not included because they were pubertal at diagnosis or their age of gonadarche was not known. The importance of prepubertal and postpubertal diabetes duration (defined as duration before or after gonadarche) is examined. The age (mean ± SD) of gonadarche was 11.4 ± 1.3 years in girls (breasts Tanner stage 2) and 12.6 ± 1.2 years in boys (testes 4 ml). A subanalysis was performed on the subgroup of 56 patients diagnosed before the age of 5 years (Dx <5 years) to determine if duration before 5 years was significant.

Methods

Stereoscopic fundus photographs were taken with a Topcon Fundus Camera (TRC 50-VT) after dilatation of the pupils with

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AER, albumin excretion rate; PreP, prepubertal; Pub, pubertal.

Table 1—*Study A: comparison of prepubertal and pubertal patients*

	Prepubertal	Pubertal	*P* value
Age of boys (years)	12.6 (12.3–13.1)	13 (12.7–13.4)	0.02
Age of girls (years)	11.8 (11.2–12.2)	12.0 (11.6–12.5)	0.08
Diabetes duration (years)	7.55 (5.1–9.7)	6.1 (4.3–7.9)	0.04
Lifetime GHb (%)	8.2 (7.8–8.7)	8.2 (7.7–8.6)	0.5

Data are median (interquartile range). Lifetime GHb results were converted to approximate HbA_{1c}. *P* value was given for GHb.

1% cyclopentolate and 2.5% phenylephrine. Nonsimultaneous photographic pairs were taken of seven standardized fields in each eye. Retinal grading was performed using an adaptation of that used by the Early Treatment Diabetic Retinopathy Study (7): in summary, level 21 (one or more hemorrhages or microaneurysms), level 31 (both hemorrhages and microaneurysms), and level 41 and 45 (moderate nonproliferative retinopathy).

AER was measured on three consecutive timed overnight urine collections. Albumin was measured using a polyclonal radioimmunoassay (Pharmacia, Uppsala, Sweden). The mean AER was used for the analysis. Elevated AER was defined as >7.5 μg/min. The 95th percentile for 690 nondiabetic Australian school children has been found to be 7.2 μg/min (8). Patients at risk of diabetic nephropathy have been identified by a rise in AER before the conventional thresholds for microalbuminuria (20 or 30 μg/min) (9–11). Patient numbers in the RESULTS section are different from those initially described because either eye slides were not gradable (study A: 9, study B: 5) or urine samples were not obtained (study A: 22, study B: 51).

GHb was measured using an in-house colorimetric method (12). The final values have been converted to approximate HbA1c percentage, using the regression equation: 1.9088 + (0.0043 × GHb). This equation was derived from simultaneous measurements using the colorimetric and high-pressure liquid chromatography Diamat (BioRad, Hercules, CA) methods. Glycemic control was analyzed as the mean of all GHb measurements available since diagnosis (median number of values: 15 for study A; 24 for study B).

Statistical analysis

The software packages of SAS (SAS Institute, Cary, NC) and SPIDA (Macquarie University, NSW, Australia) were used to analyze the data. Student's *t* test, Wilcoxon's rank-sum test, and the χ^2 test were used to compare those with and without a complication. Logistic regression was used to determine significance of predictors and to adjust for potential differences between pubertal groups.

RESULTS

Study A

There were no significant differences between the PreP and Pub groups for the presence of retinopathy: 27 (10/37) vs. 29% (38/132), *P* = 0.8. The PreP group were no less likely to have retinopathy after adjusting for sex, duration of diabetes, and GHb.

The minimum age and diabetes duration for those with retinopathy were similar: 10.3 and 2.8 years for PreP and 11.1 and 2.9 years for Pub. Retinopathy grades were as follows: level 21 in 9 (24%) PreP and 32 (24%) Pub, and level 31 in 1 (3%) PreP and 6 (5%) Pub.

There were no significant differences between the PreP and Pub groups for AER >7.5 μg/min (17 [6/35] vs. 31% [37/121], *P* = 0.1). The PreP group was no less likely to have an AER >7.5 μg/min after adjusting for sex, diabetes duration, and GHb. Mean AER was also not significantly different between PreP and Pub (4.8 vs. 5.3 μg/min, *P* = 0.5). AER >15 μg/min occurred in 2 (6%) PreP and 6 (5%) Pub (*P* = 0.9).

Study B

Retinopathy was found in 97 (52%) of 188 adolescents. Retinopathy grades were as follows: level 21 in 56 (30%), level 31 in 38 (20%), level 41 in 2 (1%), and level 45 in 1. The comparison of those with and without retinopathy is shown in Table 2. The cumulative percentage of those with retinopathy related to total and prepubertal duration is shown in Fig. 1. Using logistic regression, prepubertal duration improved the prediction for retinopathy over postpubertal duration alone (χ^2 = 17.8, *P* < 0.0005).

A significant effect of total diabetes duration to retinopathy was not found in the subgroup (Dx <5 years) (*P* = 0.083). However, when the years of diabetes before age 5 years were excluded, then duration was significant (*P* = 0.035).

AER >7.5 μg/min was found in 70 (49%) of 142 adolescents. AER >15 μg/min occurred in 24 (17%), of whom 11 (8%) had AER >30 μg/min. There was no significant effect of total diabetes duration, age, or GHb on outcome at these AER levels.

Of the 137 patients with both test results, 36 (26%) had both retinopathy and AER >7.5 μg/min.

CONCLUSIONS — The two studies presented do not support the hypothesis that prepubertal children are protected against the development of diabetes complications. In study A, there were no significant differences in the percentage of complications between prepubertal and pubertal patients ages 10–14 years. Minimum age and duration for either retinopathy or elevated albumin excretion were the same in prepubertal and pubertal patients. In study B, older adolescents with retinopathy had longer prepubertal diabetes duration than those without retinopathy.

Study A is unique in that the adolescents were of similar age and diabetes dura-

Table 2—*Study B: comparison of patients with and without retinopathy*

	Retinopathy	No retinopathy	*P* value
Boys/girls	48/53	49/38	0.2
Lifetime GHb (%)	8.6 (8.1–9.3)	8.2 (7.8–8.8)	0.049
Age at assessment (years)	17.4 (16.4–18.8)	16.4 (15.6–17.4)	0.0001
Prepubertal duration (years)	5.5 (3.6–8.3)	3.5 (1.2–6.4)	0.0006
Postpubertal duration (years)	5.5 (4.1–7.4)	4.5 (3.2–5.7)	0.0008
Total diabetes duration (years)	11.5 (9.2–13.5)	8.5 (6.0–11.7)	<0.0001

Data are *n* or median (interquartile range). Lifetime GHb results converted to approximate HbA_{1c} value. *P* value was given for GHb.

tion, with the only variable being pubertal status. Murphy et al. (4) have shown a lower percentage of retinopathy in prepubertal children (19%) compared with pubertal adolescents (33%), but their prepubertal group was younger and had shorter diabetes duration. Klein et al. (6) found a lower percentage of retinopathy in children under 13 years of age (9%) compared with a group ages 13–26 years whose diabetes was diagnosed after 13 years of age (34%), but pubertal staging was not performed.

Kostraba et al. (1), using life-table analysis, found no difference in the prevalence of retinopathy or nephropathy by postpubertal duration in postpubertal onset patients compared with prepubertal onset patients. However, no statistics are given for the possible effect of prepubertal diabetes duration on microvascular complications. Postpubertal diabetes duration was arbitrarily defined as >12 years for boys and >11 years for girls. The age of gonadarche can be quite variable, so for an analysis of the effect of postpubertal duration, each individual's onset of gonadarche should preferably be used (as in study B).

The findings in study B (Fig. 1) and the findings of Kostraba (1) may not be as disparate as first appears. We did not include any adolescents diagnosed after the onset of puberty to compare their total diabetes duration with prepubertal onset adolescents. The later stages of puberty (with higher sex steroid levels than many of our younger pubertal group in study A) may magnify these metabolic changes, thereby minimizing the preceding effect of prepubertal diabetes duration. Our sensitivity for abnormalities was lower than that used in Kostraba's study (1). The other potential confounding factor is the frequently found worsening of glycemic control associated with the psychosocial problems and hormonal changes of adolescence. The Diabetes Control and Complications Trial confirms the importance of glycemic control to the development of complications in those in at least Tanner stage 2 puberty (13).

Age, independent of sex steroids, may influence the metabolic effects of diabetes on the microvasculature. In the diabetic rat model, castrated and intact animals of the same age had the same diabetes-related kidney growth (14). Conversely, castration in rats prevents the increased leakage of radiolabelled albumin and the increases in cross-linking of collagen seen in noncastrated diabetic rats (15,16). In study B, while total duration was significant for development of retinopathy, it was not significant in the subgroup diagnosed before 5 years of age, unless duration before age 5 was excluded. This suggests that children under 5 years may be relatively immune to the development of complications.

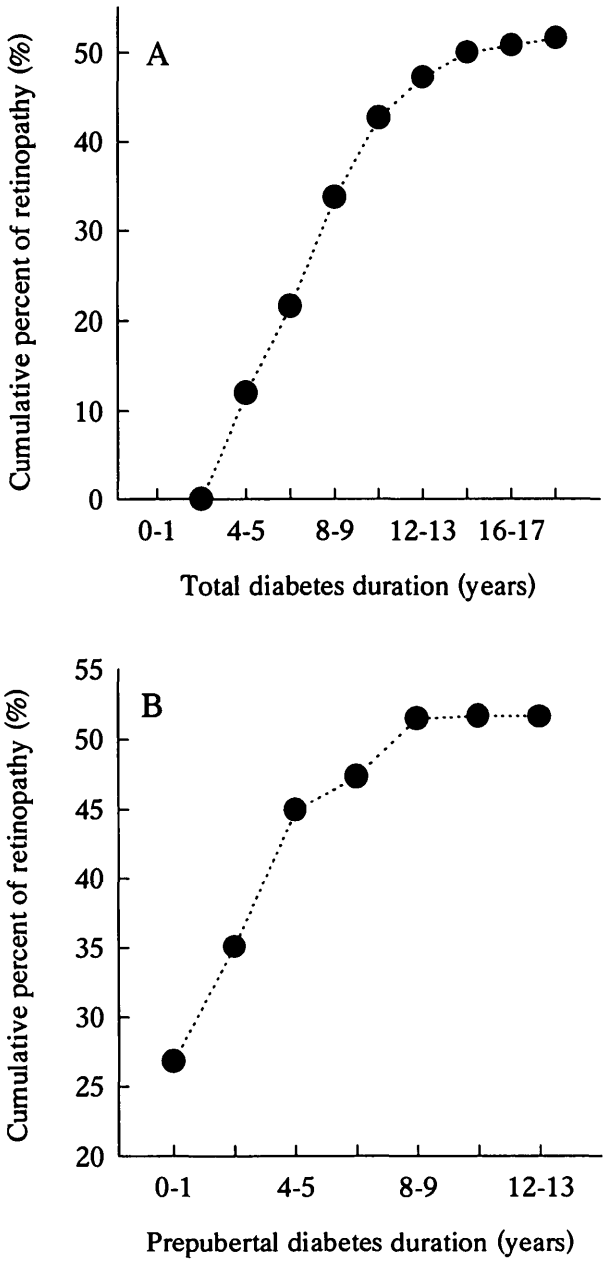

Figure 1—*Study B: cumulative cross-sectional percent of retinopathy by 2-year diabetes duration groups; total diabetes duration* (A) *and prepubertal diabetes duration* (B).

Our lack of relationship in study B between elevated albumin excretion and diabetes duration is surprising, given the very clear relationship of retinopathy to duration in the same group. Similarly, Cook and Daneman (17) found no relationship between diabetes duration and microalbuminuria in a cross-sectional study of adolescents. All patients with diabetes are at risk of retinopathy, but only a proportion are at risk of nephropathy, so the effect of duration will be diluted compared with its effect on retinopathy.

The impression that the prepubertal years of diabetes do not affect the development of complications may have influenced pediatric practices of diabetes management in prepubertal children, especially with the acknowledged risks of severe

hypoglycemia in young children (18). The current studies do not support the lack of importance of all the prepubertal years for the development of complications. More work is required to identify if the risks are uniform for all years of diabetes duration before gonadarche.

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