Do All Prepubertal Years of Diabetes Duration Contribute Equally to Diabetes Complications?

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OBJECTIVE — This study was designed to explore the timeline of protection against complications in prepubertal children with diabetes, in particular the effects of diabetes duration before age 5 years.

RESEARCH DESIGN AND METHODS — In this study, 193 adolescents with prepubertal diabetes onset were followed longitudinally for retinopathy (early background and clinical) and microalbuminuria (albumin excretion rate >7.5 µg/min and >20 µg/min). Multiple logistic regression analysis was used to compare the effect of pre- and postpubertal diabetes duration on the risk of each complication in 90 subjects reassessed as young adults. For the entire cohort, Kaplan-Meier estimates were used to determine time free of each complication, and survival was compared in those diagnosed before and after age 5 years. Accelerated failure time modeling was used to estimate the effect of covariates, including diabetes duration before puberty, on the risk of complications.

RESULTS — Prepubertal duration improved the prediction for retinopathy over postpubertal duration alone in the young adults. The survival-free period of retinopathy and microalbuminuria was significantly longer (2–4 years) for those diagnosed before age 5 years compared with those diagnosed after age 5 years. Time to onset of all complications increased progressively with longer diabetes duration before gonadarche. Higher HbA₁c during adolescence had an independent effect on the risk of retinopathy and microalbuminuria.

CONCLUSIONS — Prepubertal diabetes duration remains a significant predictor of retinopathy in young adults. The effect of time on the risk of retinopathy and microalbuminuria is nonuniform, with an increasing delay in the onset of complications in those with longer prepubertal duration. These findings are of major clinical importance when setting targets of glycemic control in young children who are at greatest risk of hypoglycemia.

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Parents and health professionals caring for very young children with diabetes must balance the opposing risks of hypoglycemia and future microvascular complications. Although the importance of avoiding severe hypoglycemia in children age <5 years is well documented (1–3), the relative contribution of these prepubertal years to the development of complications remains less certain (4).

In an earlier study using logistic regression, researchers demonstrated that longer prepubertal diabetes duration increased the risk of retinopathy, but not microalbuminuria, in adolescents (5). Studies using survival analysis have also demonstrated that the duration during prepubertal years contributes to retinopathy (6–8), and one study has demonstrated the contribution of prepubertal duration to microalbuminuria (9). Total duration as a continuous variable was not a significant predictor of microalbuminuria in a Norwegian study, but onset of diabetes before age 13 years conferred an increased risk compared to onset after age 13 years (10). In contrast, a recent study assessing urinary albumin concentration in children from the onset of diabetes demonstrated an effect of older age at diagnosis on the incidence of microalbuminuria, after adjusting for duration (11). These findings suggest that the contribution of prepubertal duration may not be uniform.

The current study was designed to explore the timeline of protection against complications in a previously reported cohort with prepubertal-onset diabetes who were followed longitudinally into adulthood. Of particular interest were the effects of diabetes duration before age 5 years and diabetes duration in time intervals before gonadarche. Accelerated failure time modeling was used because of the nonuniform effects of variables over time.

RESEARCH DESIGN AND METHODS — The study group was the previously reported cohort of 193 adolescents with diabetes (103 boys, 90 girls) whose date of gonadarche (Tanner stage two breasts or testicular volume of 4 ml) was documented in the hospital records as occurring after diabetes onset (5). Of those, 56 adolescents were diagnosed before age 5 years (median age 3.1 [2.2–4.3] years) and 137 were diagnosed after age 5 years (median age 8.4 [6.9–10.1] years). The cohort was followed longitudinally from adolescence to early adulthood. Assessments were performed.
between 1990 and 2000 at the Royal Alexandra Hospital for Children. The median number of assessments for each subject was three: 63 (33%) had one to two assessments, 65 (34%) had three to four assessments, and 41 (21%) had five to six assessments. At the time of the last assessment, 90 subjects were age >19 years; this group we defined as “young adults.” Informed consent was obtained from all participants and the study was approved by the hospital’s Ethics Committee.

Complication assessment
Retinopathy was assessed using stereoscopic fundal photography of seven fields. Early retinopathy was defined as at least one microaneurysm or hemorrhage (grade 21/10 or higher) in one eye. Clinical retinopathy was defined, as in the Diabetes Control and Complications Trial (DCCT) (12), as at least one microaneurysm and one hemorrhage in one eye and at least one microaneurysm or hemorrhage in the other eye (grade 31/21 or higher).

Albumin was measured using a polyclonal radioimmunoassay (Pharmacia AB, Uppsala, Sweden). The mean albumin excretion rate (AER) was calculated from three consecutive timed overnight urine collections. Early elevation of AER was defined as a mean AER \( \geq 7.5 \, \mu g/min \) (the 95th centile for 690 nondiabetic Australian school children was found to be 7.2 \( \mu g/min \)) (13), and microalbuminuria was defined as an AER \( \geq 20 \, \mu g/min \) in two of three samples or an albumin/creatinine ratio \( \geq 2.5 \, mg/mmol \).

HbA\textsubscript{1c} was measured at each assessment at a central laboratory using the Bio-Rad Diamat analyzer (Bio-Rad, Hercules, CA). This is a high-performance liquid chromatographic method for measuring HbA\textsubscript{1c} as a proportion of total hemoglobin. The nondiabetic range established for this method is 4–6% (mean nondiabetic HbA\textsubscript{1c} = 4.99 \pm 0.36%).

Statistical analysis
Four outcome variables were used: early and clinical retinopathy, early elevation in AER, and microalbuminuria. Because logistic regression was used in the earlier analysis (5) to investigate the effect of prepubertal diabetes duration of this cohort, we elected to use this method of analysis again in the subgroup of 90 who were now young adults (age >19 years) to allow direct comparison with our previous results. The significance of prepubertal diabetes duration for each complication was examined after adjusting for postpubertal duration and other covariates.

For the entire cohort of 193, the Kaplan-Meier estimate was used to determine median survival time for each complication; 190 had gradable photographs and 168 provided a urine specimen. In a univariate analysis, the log-rank test was used to compare survival between those diagnosed before and after age 5 years. A cutoff of age 5 years was used because those age <5 years are at greatest risk from hypoglycemia (1) and because it allowed for comparison with previous studies (11). Accelerated failure time modeling was used to estimate the effect of covariates on the risk of complications (14). Cox proportional hazards regression modeling was not used because the assumptions underlying this model, in particular that covariates are constant over time, were not met by these data. Diabetes duration was the time variable; the covariates analyzed were sex, HbA\textsubscript{1c} (as a continuous and binary variable, using the median value as a cutoff point), age at diagnosis (before or after age 5 years), three time intervals before gonadarche (diabetes onset \( \geq 5 \) years, and \( <5 \) years, and \( <2 \) years before gonadarche), insulin dosage per kilogram, and number of injections per day (two versus three or more). Nonsignificant variables were excluded from the model. Statistical analysis was performed using STATA, version 6.0, and SPSS, version 10.0.

Results are expressed as medians and interquartile range (IQR). The odds ratio (OR) and 95% CI are reported for logistic regression analysis. The time ratio (TR) and 95% CI are reported for accelerated failure time modeling. The TR is the time to onset of an event, after adjusting for other variables in the model.

RESULTS
Final assessment as young adults
Data were available on 90 individuals age >19 years (47% of the original cohort). Their median age was 21.7 (20.3–23.7) years and median diabetes duration was 15.6 (12.6–17.9) years. Their median HbA\textsubscript{1c} at this final assessment was 8.3% (7.2–9.6%). This group did not differ significantly in age, diabetes duration (pre- or postpubertal), socioeconomic status, previous HbA\textsubscript{1c}, or complications status at the time of the previous report (5) from the 103 not reassessed. At this latest time point, early retinopathy was present in 75%; clinical retinopathy in 36% (three had required laser treatment); AER \( \geq 7.5 \, \mu g/min \) in 41%; and microalbuminuria in 14%.

Using multiple logistic regression and after adjusting for HbA\textsubscript{1c}, the risk for clinical retinopathy increased by 28% for every prepubertal year of duration (OR 1.28 [1.08–1.53]) and by 36% for every postpubertal year of diabetes duration (OR 1.36 [1.10–1.69]). Inclusion of postpubertal duration in the model improved the prediction for clinical retinopathy, with all three variables (HbA\textsubscript{1c} and pre- and postpubertal duration) together accounting for 14.9% of the variation (\( r^2 = 5.8\% \) in the model without prepubertal duration, likelihood ratio test \( P < 0.001 \)). Age was not significant in the model. Findings were similar for early or clinical retinopathy: prepubertal duration OR 1.25 (1.04–1.49) and postpubertal duration OR 1.45 (1.13–1.86). Only higher HbA\textsubscript{1c} (but neither age nor duration) increased the risk for elevated AER (OR 1.42 [1.02–1.97]) and for microalbuminuria (OR 1.36 [1.04–1.78]).

Survival analysis
The median survival time in the 193 subjects was 9.7 (7.7–13.3) years to onset of early retinopathy, 14.9 (12.6–18.7) years for clinical retinopathy, 11.1 years (9.3–18.2) for AER \( \geq 7.5 \, \mu g/min \), and 21.2 years for microalbuminuria (the IQR could not be defined for microalbuminuria as so few had reached this end point).

The subgroup diagnosed before age 5 years had significantly longer time to onset of the four outcomes compared to those diagnosed after age 5 years (Figs. 1 and 2). The median survival times were 12.2 vs. 8.9 years for retinopathy (\( P < 0.0001 \)), 15.9 vs. 13.2 years for clinical retinopathy (\( P = 0.002 \)), and 13.8 vs. 9.5 years for AER \( \geq 7.5 \, \mu g/min \) (\( P = 0.0002 \)), respectively. Time to onset of microalbuminuria was significantly longer in those diagnosed before age 5 years (\( P = 0.02 \)).

Accelerated failure time model
Effect of diabetes duration before age 5 years. Time to onset of early retinopathy was 33% longer in those diagnosed before age 5 years (TR 1.33 [1.23–1.43]) and 7% shorter with HbA\textsubscript{1c} \( \geq 8.4\% \) (TR 0.93
Time to onset of clinical retinopathy was 29% longer in those diagnosed before age 5 years (TR 1.29 [1.17–1.42]) and 10% shorter with higher HbA1c (TR 0.90 [0.82–0.98]). Time to onset of AER/7.5/9262 g/min was 43% longer in those diagnosed before age 5 years (TR 1.43 [1.27–1.62]) and 15% shorter with higher HbA1c (TR 0.85 [0.77–0.94]). Time to onset of microalbuminuria was 47% longer in those diagnosed before age 5 years (TR 1.47 [1.33–1.63]) and 6% shorter with higher HbA1c (TR 0.94 [0.88–0.99]).

**Effect of diabetes duration before gonadarche.** Time to onset of all four outcomes was significantly longer in subjects with diabetes duration ≥5 years before gonadarche (Table 1). Time to onset of clinical retinopathy was 39% longer (for any retinopathy, 48% longer) for patients with ≥5 years compared to those with <2 years of duration before gonadarche. Similarly, time to onset of microalbuminuria was 56% longer (and 81% longer for AER ≥7.5 µg/min) for patients with ≥5 years compared to those with <2 years duration before gonadarche. Higher HbA1c had an independent effect on time to onset of complications: the group with HbA1c ≥8.4% had a shorter time to onset of complications by 8–21%.

**CONCLUSIONS** — This study demonstrated a nonuniform effect of diabetes duration for microvascular complications in prepubertal onset subjects followed longitudinally into late adolescence and adulthood. The effects of pre- and postpubertal diabetes duration were compared using logistic regression in those followed into adulthood, and survival analysis was used to further explore the predictors of complications in the whole cohort.

In the subgroup of young adults, the continuing significance of prepubertal diabetes duration as a predictor of any retinopathy and clinical retinopathy was confirmed. When examined as adolescents in our earlier study (5), prepubertal duration improved the prediction for retinopathy over postpubertal duration alone. When reexamined as young adults (median duration 15.6 years), the effect of prepubertal duration could now be more adequately compared with that of postpubertal duration. The risk increment for clinical retinopathy was smaller for each year of prepubertal duration compared to each year of postpubertal duration (28 vs. 36%) using logistic regression.

These findings are in agreement with the Berlin Retinopathy Study in which time to onset of retinopathy was compared between patients with pre- and postpubertal onset of diabetes. The median postpubertal duration until incipient retinopathy (defined as 1–10 microaneurysms) was ~3 years shorter in those with prepubertal onset diabetes (7). However, incipient retinopathy developed after shorter total diabetes duration in adolescents with pubertal-onset diabetes, indicating that each pubertal year had a greater impact than the prepubertal years (15).

The relative effects of pre- and postpubertal diabetes duration on microalbuminuria could not be compared in the smaller subgroup followed as adults because neither duration was significant in the logistic regression model. However, the relative effects of duration before and after age 5 years were demonstrated using survival analysis in the total group. A significant effect of diabetes duration on the risk of microalbuminuria has been found by some groups (16), but other groups have failed to demonstrate a relation in adolescents (17). In an earlier study of 937 adolescents (18), the authors found that duration accounted for 14% of the variation for clinical retinopathy compared to 6% for microalbuminuria. This indicated that total duration has a smaller effect on the risk of microalbuminuria, and that other factors such as HbA1c (as...
shown in this study) may be more important.

Any study of complications in adolescents and young adults requires surrogate end points that may be reversible, such as microalbuminuria >20 μg/min (19,20) and clinical retinopathy (21). Because in our study only a small proportion of adolescents or young adults (14%) had reached the end point of microalbuminuria, a mean AER ≥7.5 μg/min was also used in this analysis. Borderline elevations in AER have been shown to predict progression to persistent microalbuminuria in adults (22,23) and adolescents (24).

Survival analysis explores the time to onset of an end point. Using a cutoff age of 5 years at diagnosis enabled comparison of duration before and after that age on microvascular complications. Comparison of these two groups using the log-rank test demonstrated a significantly longer time to onset of complications (2–4 years) in those diagnosed before age 5 years. This could be explained by the relatively longer prepubertal duration of the individuals diagnosed before age 5 years. Given that we confirmed that postpubertal diabetes duration had a greater effect on retinopathy than prepubertal duration using logistic regression, it was indeed appropriate to use accelerated failure time modeling to account for the non-uniform effects of time.

Accelerated failure time modeling confirmed a significantly longer time to development of complications in the child with diabetes before age 5 years (and the child diagnosed >5 years before onset of his or her gonadarche). The time to onset of complications was longer for children diagnosed at least 5 years before onset of gonadarche compared to diagnosis within 2 years of gonadarche, being 39–48% longer for retinopathy and even longer (56–81%) for elevated AER. Before age 5 years, the gonadal and adrenal axes are relatively inactive, but between age 5 years and the onset of gonadarche, adrenal androgen levels steadily increase (25). However, in an earlier study of prepubertal children ages 8–9 years, the children with early retinopathy actually had significantly lower levels of dehydroepi-

![Figure 2](image)

**Figure 2**—Survival-free period of AER ≥7.5 μg/min and microalbuminuria in subjects diagnosed before and after age 5 years (log-rank test, P < 0.001 and P = 0.0004, respectively).

<table>
<thead>
<tr>
<th>Diabetes duration before gonadarche*</th>
<th>Early retinopathy</th>
<th>Clinical retinopathy</th>
<th>AER ≥7.5 μg/min</th>
<th>AER ≥20 μg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;5 years</td>
<td>1.13 (0.97–1.31)</td>
<td>1.20 (1.06–1.34)</td>
<td>1.05 (0.84–1.31)</td>
<td>1.34 (1.14–1.58)</td>
</tr>
<tr>
<td>≥5 years</td>
<td>1.39 (1.22–1.59)</td>
<td>1.48 (1.34–1.63)</td>
<td>1.56 (1.27–1.90)</td>
<td>1.81 (1.60–2.04)</td>
</tr>
<tr>
<td>HbA1c ≥8.4%†</td>
<td>0.92 (0.85–1.00)</td>
<td>—</td>
<td>0.79 (0.68–0.93)</td>
<td>0.89 (0.82–0.97)</td>
</tr>
<tr>
<td>≥3 injections‡</td>
<td>—</td>
<td>0.89 (0.83–0.95)</td>
<td>—</td>
<td>0.86 (0.77–0.95)</td>
</tr>
<tr>
<td>Insulin dosage/kg</td>
<td>0.82 (0.75–0.91)</td>
<td>0.81 (0.74–0.89)</td>
<td>0.80 (0.72–0.89)</td>
<td>0.76 (0.69–0.85)</td>
</tr>
</tbody>
</table>

Data are time ratios (95% CI). *Compared with onset <2 years before gonadarche; †compared with HbA1c <8.4% (median for group); ‡compared with <3 injections.
Prepubertal diabetes and complications

...androstenedione than those without retinopathy (0.2 vs. 1.1 μmol/l) (26). Growth hormone levels rise after gonadarche onset, and may be the major accelerator of diabetes microvascular disease (27). Therefore, the child with longer diabetes duration before peak growth hormone production is likely to be at lower risk in the prepubertal period.

The current study was the first to quantify the relative risk of different time periods before gonadarche. The longer time seen to onset of AER and microalbuminuria in the young child extends the initial findings from the Joslin Clinic study, in which the later end point of persistent proteinuria was used (28). When subdivided based on age at diagnosis (0–9, 10–14, and 15–20 years), there was a longer time to onset of proteinuria in those with diabetes onset at an earlier age, indicating that prepubertal duration had a lesser effect. In the Oxford Regional Prospective Study, there appeared to be a longer latent period before onset of microalbuminuria in children diagnosed age <5 years compared to those diagnosed at ages 5–11 years and >11 years (11).

HbA1c at the time of assessment had an independent effect on the risk of microvascular complications after adjusting for diabetes duration. Our data were not intended to explore the effect of prepubertal glycemic control on microvascular disease. However, the model did demonstrate an effect of HbA1c in pubertal years on the time to complication outcomes that was independent of age at diagnosis (and all were diagnosed before puberty). An elevated HbA1c during adolescence accelerated the time to onset of complications by 8–21%, whereas a younger age of diagnosis (and longer duration before puberty) slowed the time to onset by 39–81%. This observation is of particular clinical relevance for those caring for children and adolescents. It complements the DCCT finding that intervening to improve diabetes control reduces the risk of complications independently of previous glycemic control (12).

This study confirms that the prepubertal years of diabetes duration are significant for the development of retinopathy. However, the time taken to develop any of the microvascular end points was significantly longer for prepubertal children diagnosed before age 5 years compared to those diagnosed after that age. This implies a greater degree of protection from later microvascular complications in the very young child. These findings are of major clinical importance for management goals of metabolic control given the risks of hypoglycemia in very young children.

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References


