

Early Glycemic Control, Age at Onset, and Development of Microvascular Complications in Childhood-Onset Type 1 Diabetes

A population-based study in northern Sweden

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OBJECTIVE — The aim of this work was to study the impact of glycemic control (HbA_{1c}) early in disease and age at onset on the occurrence of incipient diabetic nephropathy (MA) and background retinopathy (RP) in childhood-onset type 1 diabetes.

RESEARCH DESIGN AND METHODS — All children, diagnosed at 0–14 years in a geographically defined area in northern Sweden between 1981 and 1992, were identified using the Swedish Childhood Diabetes Registry. From 1981, a nationwide childhood diabetes care program was implemented recommending intensified insulin treatment. HbA_{1c} and urinary albumin excretion were analyzed, and fundus photography was performed regularly. Retrospective data on all 94 patients were retrieved from medical records and laboratory reports.

RESULTS — During the follow-up period, with a mean duration of 12 ± 4 years (range 5–19), 17 patients (18%) developed MA, 45 patients (48%) developed RP, and 52% had either or both complications. A Cox proportional hazard regression, modeling duration to occurrence of MA or RP, showed that glycemic control (reflected by mean HbA_{1c}) during the follow-up was significantly associated with both MA and RP when adjusted for sex, birth weight, age at onset, and tobacco use as potential confounders. Mean HbA_{1c} during the first 5 years of diabetes was a near-significant determinant for development of MA (hazard ratio 1.41, *P* = 0.083) and a significant determinant of RP (1.32, *P* = 0.036). The age at onset of diabetes significantly influenced the risk of developing RP (1.11, *P* = 0.021). Thus, in a Kaplan-Meier analysis, onset of diabetes before the age of 5 years, compared with the age-groups 5–11 and >11 years, showed a longer time to occurrence of RP (*P* = 0.015), but no clear tendency was seen for MA, perhaps due to lower statistical power.

CONCLUSIONS — Despite modern insulin treatment, >50% of patients with childhood-onset type 1 diabetes developed detectable diabetes complications after ~12 years of diabetes. Inadequate glycemic control, also during the first 5 years of diabetes, seems to accelerate time to occurrence, whereas a young age at onset of diabetes seems to prolong the time to development of microvascular complications.

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Abbreviations: AGE, advanced glycation end product; DCCT, Diabetes Control and Complications Trial; MA, incipient diabetic nephropathy (persistent microalbuminuria); RP, background retinopathy.

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

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Long-term glycemic control and diabetes duration are well-known risk factors for the development of microvascular complications in type 1 diabetes, and it has also been shown that intensive insulin treatment and improved glycemic control delays the onset and slows the progression of these complications (1,2). Hyperglycemia is a necessary but not sufficient factor for development of diabetic nephropathy (3), whereas hyperglycemia seems to be the major risk factor for proliferative retinopathy (4). Other factors such as familial or genetic predisposition and perinatal factors may contribute (5,6). It is also hypothesized that diabetic microangiopathy in different organs is genetically heterogeneous (4) because, given sufficient diabetes duration, retinopathy is almost universal, but not all patients develop nephropathy (7). Neither will patients with nephropathy invariably have concomitant retinopathy (8). The risk factors involved in the development and progression are not identical for these two microvascular complications (9).

Puberty is a period of rapid growth and hormonal changes and is often characterized by a deterioration in glycemic control, and all of these factors may promote the development of diabetes complications (10,11). It has been discussed whether early, prepubertal, glycemic control contributes to the development of microvascular complications to a lesser degree than in later stages (12). On the other hand, growing evidence shows that microvascular complications can occur early even in the prepubertal years (13–15) and that both short- and long-term glycemic control may be of importance (16).

The aim of this study was to estimate the occurrence of incipient diabetic nephropathy (MA) and background retinopathy (RP) in a group of young patients with type 1 diabetes treated according to a standardized diabetes care program. We

also wanted to study the impact of early versus late glycemic control as well as age at onset after adjustments for other potential risk factors such as disease duration, tobacco use, birth weight, and sex.

RESEARCH DESIGN AND METHODS

Ninety-four children, ages 0–14 years old at onset of type 1 diabetes, who all initially were diagnosed and treated at the Department of Pediatrics at the Umeå University Hospital between 1981 and 1992, were identified through the Swedish Childhood Diabetes Registry, which covered 96–99% of all incident childhood-onset diabetes cases in Sweden (17). All children with type 1 diabetes in a geographically defined area were admitted to the hospital, and thus, this is considered a population-based study.

The city of Umeå is situated in the county of Västerbotten in northern Sweden at 62°N. The area of Västerbotten is 15,093 km² with ~200,000 inhabitants. Umeå is the largest city and has ~100,000 inhabitants. The Department of Pediatrics at the University Hospital in Umeå covers ~75% of the pediatric population in the county of Västerbotten (Umeå and Lycksele), which is an area with ~30,000 children <15 years of age.

The treatment followed a nationwide childhood diabetes care program (18), and from 1981, HbA_{1c} was measured every 3–4 months. The diabetes care program recommended eye examinations (fundus photography) in children to begin at 10 years of age independently of diabetes duration, at diagnosis in children >10 years of age, and then every second year if no lesions were seen. Screening for microalbuminuria was recommended yearly after >5 years of diabetes duration or after 12 years of age. Intensified insulin treatment, using multiple injections or insulin pumps, was also recommended and generally adopted. Data on these patients were retrieved from medical records and laboratory reports from the Departments of Pediatrics and Internal Medicine, where the patients were later followed up. Typically, the patients were referred at 19–20 years of age. Information on gestational age, birth weight, and birth length was collected from the Swedish Medical Birth Registry. For patients born before 1973, this information was collected from birth records from the hospitals in the county of Västerbotten. In

January 2002, 93 of the patients were alive. One patient had died suddenly in bed at 17 years of age after 12 years of diabetes duration and had at that time no signs of microvascular complications. The study was approved by the Research Ethics Committee of Umeå University.

Diagnosis of nephropathy

We defined incipient nephropathy as follows: at least two of three consecutive overnight urine samples with albumin excretion rate 20–199 µg/min or an early morning sample with albumin concentration of 30–299 mg/l. Overt nephropathy was defined as ≥200 µg/min or ≥300 mg/l (19,20). The urine samples should be collected at a time interval of 6–12 months and the results documented in medical records or laboratory reports. There should be no indication of any other renal disease according to results from urine dipsticks or in the medical history. One of the investigators (M.S.) verified all the diagnoses of incipient nephropathy by scrutinizing medical records with respect to clinical data and laboratory reports. Onset of microalbuminuria was defined as the day when the first of two albumin-positive samples was collected.

Diagnosis of retinopathy

The patients were screened for retinal lesions according to the diabetes care program. Standardized screening photographs were taken after dilatation of the pupil and included two fields for each eye (the disk and macular). These photographs were assessed and judged by a skilled ophthalmologist (20). The results from these examinations were obtained from medical records from the Department of Ophthalmology. The first recording of any diabetes-related retinal lesion, commonly microaneurysms, was regarded as onset of RP.

Other clinical characteristics

Tobacco use was defined as current or previous tobacco use as recorded in medical records. No patient smoked or used snuff when diabetes was diagnosed. Birth weight and length were adjusted for gestational age and sex by using an SD score; an SD score of 0 represents the 50th centile, and 1.64 represents the 95th centile. Because data on pubertal stage, according to Tanner and in growth charts, was poorly described in medical records and

because we wanted to study prepubertal age-groups, we used age 11 years as a proxy for the onset of puberty in both sexes. This is in accordance with other studies (15,21).

Blood and urine chemistry

The mean HbA_{1c} level during the first 5 years of diabetes was used as a reflection of “early” glycemic control, and the period after 5 years of diabetes was defined as “late” glycemic control. HbA_{1c} was followed to the onset of MA or RP or during the entire follow-up in patients without complications. The range of HbA_{1c} for the total population, during the entire follow-up period or until onset of MA or RP, was used to stratify the study population as having “poor” and “fair” metabolic control. “Poor” control (HbA_{1c} ≥8.2%) was the top quartile of the distribution of the mean HbA_{1c}, and “fair” (HbA_{1c} ≤7.4%) was the lower two quartiles. This definition gives a glycemic level in which “poor” is ≥9.2% and “fair” is ≤8.4% when adjusting to Diabetes Control and Complications Trial (DCCT) standards.

All HbA_{1c} samples used in this study were analyzed at the Department of Clinical Chemistry, Umeå University Hospital. Between 1981 and 1985, HbA_{1c} was analyzed by using an isoelectrical focusing technique (normal range 5–8%) (22), and thereafter until 1991, glycosylated hemoglobin was analyzed by using chromatography on boronate agarose gel (Glycoglobin Kit; Endocrine Sciences Products) (normal range 4.2–6%). Between 1991 and 1997, HbA_{1c} was measured by high-pressure liquid chromatography (Integral 4000; BioRad, Anaheim, CA) (normal range 3.2–4.7%) (23). In 1997, a nationwide calibration of HbA_{1c} analyses was made (Equalis Reference Swedish Laboratory), and the normal range in our laboratory was changed to 3.6–5.0%. All HbA_{1c} values in the study were adjusted to be in accordance with this method by using regression equations among the different methods (1981–1985 $y = 0.515x + 0.872$; 1985–1991 $y = 0.643x + 0.743$; 1991–1997 $y = 1.0379x + 0.1$ in which y is the HbA_{1c} value according to the present method used). A mean HbA_{1c} during the early, late, and entire follow-up period was then estimated for each patient and was weighted for the time between the measurements (24). The HbA_{1c} range in this study is approximately one percent-

Table 1—Clinical and biochemical characteristics at follow-up among patients with and without MA and RP, respectively

	MA	No MA	P	RP	No RP	P
n	17	77		45	49	
Sex						
Boys	11 (65)	36 (47)	0.28	21 (47)	26 (53)	0.68
Girls	6 (35)	41 (53)		24 (53)	23 (47)	
Birth weight (SD score)	-0.66 to 1.48	-1.34 to 1.74	0.12	-0.91 to 1.00	-1.34 to 1.74	0.52
Diabetes onset (years)	8.7 ± 2.9	9.0 ± 3.9	0.77	9.1 ± 3.7	8.8 ± 3.7	0.71
Age of onset of diabetes						
<5 years	2 (12)	15 (88)	0.31	7 (41)	10 (59)	0.78
5–11 years	11 (25)	34 (75)		23 (49)	22 (51)	
>11 years	4 (12)	28 (88)		15 (47)	17 (53)	
Diabetes duration (years)	13.7 ± 3.4 (7.2–18.5)	11.4 ± 3.3 (5.2–18.9)	0.01	13.5 ± 3.2 (7.2–18.9)	10.2 ± 2.9 (5.2–17.1)	<0.01
Tobacco use	1 (6)	7 (9)	1.00	6 (13)	2 (4)	0.15
Mean HbA _{1c} (%) during entire follow-up period	7.9 ± 1.2 (5.5–10.0)	7.4 ± 1.1 (4.8–10.2)	0.13	7.9 ± 1.1 (5.5–10.9)	7.1 ± 1.1 (4.8–9.9)	0.02
Mean HbA _{1c} (%) first 5 years of diabetes	7.3 ± 1.2 (5.2–9.8)	7.0 ± 1.3 (4.3–10.2)	0.33	7.3 ± 1.2 (5.2–10.2)	6.8 ± 1.3 (4.3–10.1)	0.031
Mean HbA _{1c} (%) after 5 years of diabetes	8.8 ± 1.9 (5.6–11.7)	7.7 ± 1.3 (5.1–11.0)	0.008	8.2 ± 1.6 (5.1–12.1)	7.7 ± 1.4 (5.6–11.7)	0.12
BMI (kg/m ²)*	22.8 ± 2.2 (19.4–26.8)	23.3 ± 2.5 (18.0–27.9)	0.43	23.2 ± 2.4 (18.6–26.8)	23.3 ± 2.5 (18.0–27.9)	0.89
Mean arterial blood pressure (mmHg)*	89.4 ± 10.3 (62–102)	89.5 ± 6.5 (78–110)	0.98	90.1 ± 8.6 (62–110)	88.6 ± 5.3 (79–98)	0.40

Data are means ± SD (range) or n (%); *At 18 years of age, numbers of patients with information on these variables were 74 for BMI and 71 for blood pressure.

age unit lower as compared with the DCCT standard (25).

Urine analyses between the years 1981 and 1994 were performed by immunological nephelometric analysis (26), and from 1994, immunoturbidometry (27) is used at the Department of Clinical Chemistry, Umeå University Hospital. The two methods have similar detection limits and correlate well with each other.

Statistical methods

Differences in mean values between groups were analyzed with the Student's two-tailed *t* test, and proportions were tested using Fisher's exact test. One-way ANOVA was used to test differences among age-at-onset groups. Data are presented as mean ± SD or as indicated. Cox proportional hazard analysis was used to adjust for duration of diabetes and to assess the potential influence of different confounding variables on the occurrence of MA and RP. Kaplan-Meier survival analysis with log-rank test for trends was used to estimate the probability of developing MA or RP in different age-groups. A *P* value <0.05 was considered statistically significant. Results are given with their 95% CIs. SPSS 10.0 Macintosh version (Software MacKiev Company, Cupertino, CA) was used to analyze data.

RESULTS

Clinical characteristics

The annual incidence of type 1 diabetes in northern Sweden in children 0–14 years of age is now ~31/100,000. During the time period 1981–1992, there has been an increase in the annual incidence from 19 to 31/100,000 in northern Sweden. This is similar to the rest of Sweden (The Swedish Childhood Diabetes Study Group, unpublished data). The mean annual incidence in our study was 28/100,000, which is similar and indicates that all children in the area were identified.

For all patients, the mean diabetes duration at follow-up was 11.8 ± 3.5 years (range 5–19), the mean age at onset of diabetes was 8.9 ± 3.7 years (0.8–14.5), and mean HbA_{1c} was 7.5 ± 1.2% (range 4.8–10.2%). Among patients who had no signs of either MA or RP (*n* = 45), the mean diabetes duration was significantly shorter than in patients with any microvascular complication: 10.1 ± 2.9 vs. 13.4 ± 3.2 years (*P* < 0.001). The median number of HbA_{1c} measurements for all patients was 38 (range 8–72). The median number of eye and kidney examinations was 4 (range 0–11) and 9 (range 0–39), respectively. A strong correlation

was found between the numbers of eye examinations and follow-up time (*P* < 0.0001) but not for kidney examinations (*P* = 0.280). No association was found between the number of examinations and glycemic level (mean HbA_{1c}) (*P* = 0.081 and *P* = 0.601, respectively) when adjusting for diabetes duration. All children in this study had been examined at least according to these recommendations, and many were examined somewhat earlier and at a closer interval.

Seventeen (18%) of the 94 patients fulfilled the criteria for MA during the follow-up period. None of the patients developed overt nephropathy, elevated serum creatinine, or had signs of any other kidney disorder, e.g., hematuria, during the follow-up period. Seven (41%) of the patients with microalbuminuria were treated with ACE inhibitors. The mean time to diagnosis of MA was 9 ± 3 years (range 4–15) from diabetes onset. Forty-five (48%) of the 94 patients fulfilled the criteria for RP during the follow-up period. None of the patients developed proliferative retinopathy or were treated with photocoagulation. The mean time to diagnosis of RP was 11 ± 4 years (range 4–19) from onset of diabetes. Of the 45 patients with RP, 13 (29%) had concomitant MA, and thus 13

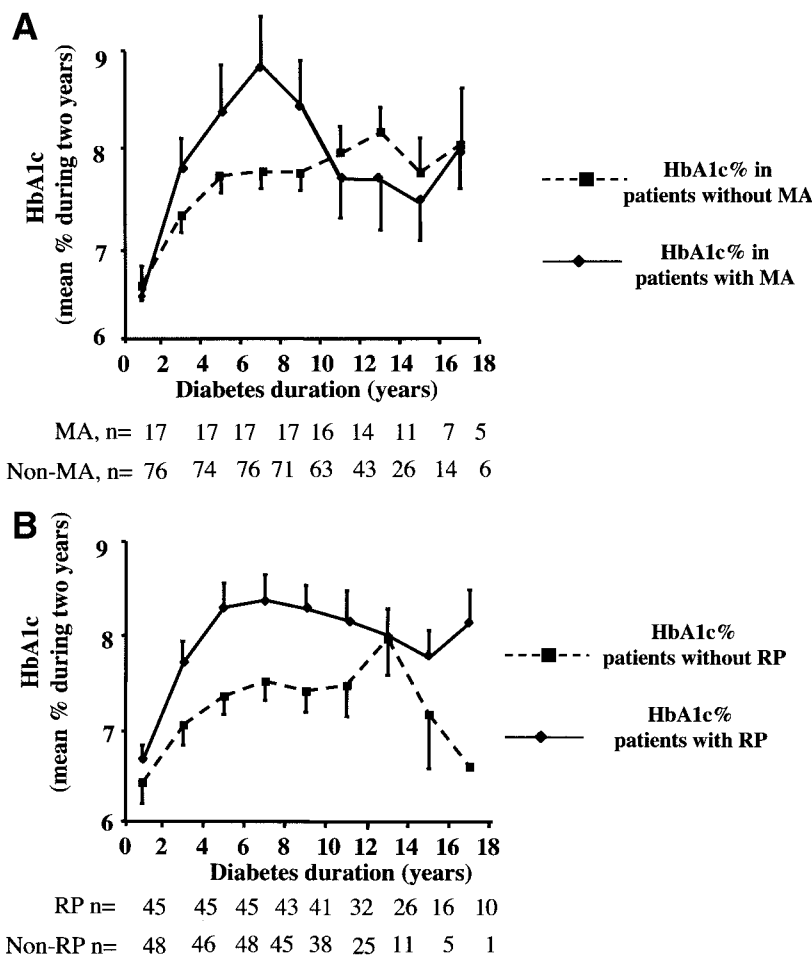


Figure 1—Glycemic level (mean HbA_{1c} %) every second year of diabetes duration divided into patients with and without MA (A) and RP (B) at follow-up, respectively, presented as mean ± SE. n, number of patients in each group followed to the indicated time.

(76.5%) of the 17 patients with MA had concomitant RP. Table 1 shows clinical data on patients with and without MA or RP, respectively. Altogether, among the 94 patients, 32 (34%) had isolated RP, 4 (4%) had isolated MA, and 13 (14%) had combined RP and MA. Thus, 49 (52%) patients had either one or both complications and, hence, 45 (48%) had neither of these complications.

Glycemic control over time

Figure 1 shows the mean HbA_{1c} levels ± SE over the total follow-up time in patients with and without MA and RP, respectively. The mean HbA_{1c} level tended to be higher during the entire follow-up period among patients who developed RP, whereas in patients who developed MA, this was obvious only during the first 10 years. After 10 years of follow-up, there was a marked decreased in HbA_{1c}

levels in patients who developed MA, which was a decrease in mean HbA_{1c} that was not paralleled in any of the other groups.

However, when calculating an updated mean of annual measurements of

HbA_{1c} (glycemic exposure) (28), the HbA_{1c} level tended to be higher during the entire follow-up period both among patients who developed MA and those who developed RP when compared with patients without any microvascular complication (data not shown).

Multivariate analyses

To adjust for differences in diabetes duration among patients with and without MA and RP, respectively, and other potential risk factors, i.e., sex, low birth weight, age at onset of diabetes, and smoking, Cox proportional hazard regression models were designed for the three different periods of glycemic control. Results are shown in Tables 2 and 3.

When using an updated mean of annual measurements of HbA_{1c} instead of the calculated glycemic level over time in these models, only minor, nonsignificant differences were found that did not alter the overall results (data not shown).

Incipient diabetic nephropathy

When modeling MA as a function of glycemic level up to the onset of MA or during the entire follow-up period, adjusting for sex, birth weight, age at onset of diabetes, and tobacco use, only glycemic control had a significant effect. An increase in hazard ratio (HR) of 83% per one percentage unit increase in mean HbA_{1c} was seen. When early glycemic level (<5 years of diabetes duration) was considered, this estimate was nearly significantly associated (P = 0.0.83) and had an increase in HR of 41%. Whereas when using an estimate for late glycemic control after 5 years, until the onset of MA or during the entire follow-up period, a statistically significant effect was seen for onset

Table 2—Cox proportional hazard of risk factors for developing MA

Variable	Glycemic level during the entire follow-up period		Glycemic level during 0–5 years of diabetes		Glycemic level during >5 years of diabetes	
	Hazard rate	95% CI	Hazard rate	95% CI	Hazard rate	95% CI
Glycemic level (HbA _{1c} , %)	1.83	1.06–3.16	1.41	0.96–2.08	1.45	1.05–2.00
Sex (boys vs. girls)	2.85	0.93–8.70	2.15	0.75–6.10	1.55	0.55–4.38
Birth weight (SD score)	2.13	0.92–5.03	2.00	0.85–4.68	1.86	0.76–4.55
Age at onset (years)	1.03	0.91–1.17	1.05	0.93–1.19	1.04	0.92–1.19
Tobacco use (yes vs. no)	0.57	0.07–4.63	0.71	0.09–5.74	0.82	0.10–6.61

Table 3—Cox proportional hazard of risk factors for developing RP

Variable	Glycemic level during the entire follow-up period		Glycemic level during 0–5 years of diabetes		Glycemic level during >5 years of diabetes	
	Hazard rate	95% CI	Hazard rate	95% CI	Hazard rate	95% CI
Glycemic level (HbA _{1c} , %)	1.43	1.06–1.94	1.32	1.02–1.71	1.01	0.85–1.21
Sex (boys vs. girls)	0.87	0.45–1.66	0.87	0.46–1.67	0.90	0.47–1.70
Birth weight (SD score)	1.26	0.74–2.16	1.13	0.66–1.92	1.00	0.59–1.69
Age at onset (years)	1.11	1.02–1.20	1.10	1.02–1.20	1.11	1.03–1.21
Tobacco use (yes vs. no)	1.15	0.41–3.22	1.26	0.46–3.50	1.39	0.51–3.75

of MA ($P = 0.025$) with an increase in HR of 45%.

Background retinopathy

The glycemic level until detection of RP or during the entire period and the first 5 years of diabetes (early) had significant effects ($P = 0.020$, $P = 0.036$) on development of RP. The increase in HR of developing RP for each percentage unit rise in HbA_{1c} during the entire follow-up period was 43% and in the early period 32%. However, late glycemic level was not a significant determinant of RP ($P = 0.897$) probably due to low statistical power. Age at onset of diabetes was a weak but significant independent determinant for the development of RP in all regression models ($P = 0.015$, $P = 0.018$, and $P = 0.010$, respectively).

Effect of early glycemic control on MA and RP

Models of the cumulative hazard rates for development of MA and RP as functions of “poor” (HbA_{1c} $\geq 8.2\%$) or “fair” (HbA_{1c} $\leq 7.4\%$) glycemic control during the entire follow-up, the early period, and the late period were constructed. Significant differences for the development of MA were seen between groups when the late ($P = 0.026$) (data not shown) or the entire follow-up ($P = 0.030$) period was considered (Fig. 2A). For RP, a significant difference between groups was found during the entire follow-up ($P = 0.001$) period (Fig. 2B) but not when the early ($P = 0.435$) or the late ($P = 0.677$) period was entered separately into the model (data not shown). A near-significant difference for development of MA between groups was seen when the early ($P = 0.061$) period was entered into the model (Fig. 2C).

Effect of age at onset on MA and RP

We also studied the effect of age at onset on the development of MA and RP by dividing the patients into three groups: those who were <5 years ($n = 17$), 5–11 years ($n = 42$), and >11 years ($n = 35$) of age, respectively, at diagnosis. A significant difference in mean diabetes duration was seen among age-at-onset groups (13.7 ± 3.6 , 11.8 ± 3.1 , and 10.8 ± 3.5 years, respectively, $P = 0.019$), with the youngest age-group having the longest follow-up. No significant differences in mean HbA_{1c} during follow-up ($P = 0.252$) was seen among the age-at-onset groups. A significant difference in the number of kidney ($P = 0.009$) but not eye ($P = 0.912$) examinations was found among the age-at-onset groups.

Kaplan-Meier analyses of the cumulative probability of developing MA and RP, as function of age at onset, were then calculated. There were no differences between groups when MA was considered, but a diagnosis of diabetes before the age of 5 years significantly prolonged the time to RP, compared with the age-groups 5–11 and >11 years ($P = 0.015$), as shown in Fig. 3.

The impact of overall and early glycemic level and age at onset of diabetes for the development of any microvascular complication (MA and/or RP) and for combined complications (MA and RP) were also analyzed. These findings were very similar to those described above for MA and RP, respectively, because the vast majority with MA also had RP.

CONCLUSIONS— In this retrospective study of the occurrence of early microvascular complications, i.e., incipient MA and RP, in a group of patients with childhood-onset type 1 diabetes, 18% de-

veloped MA and 48% RP during a mean follow-up of ~ 12 years, and this occurred despite modern insulin treatment. This is in accordance with other comparable studies in children and adolescents (15,29–32). However, a lower occurrence of renal involvement and retinopathy after ~ 10 years in a nationwide study has been found in patients with onset of diabetes in young adulthood (15–34 years) (33,34). Despite that this study was relatively small and had a retrospective design, we were able to show that the glycemic level already during the first 5 years may be an important predictor of later development of both MA and RP. This is in accordance with previous prospective follow-up studies (16,30).

The mechanism behind the effect of early glycemic level on MA is unclear, but it could be speculated that the effect of hyperglycemia to promote early glomerular hyperfiltration (19,35) is partly responsible. The early glomerular hyperfiltration seen in some, but not all, patients at the onset of type 1 diabetes has been shown to predict both incipient and overt diabetic nephropathy (19,35,36). It has been hypothesized that glomerular hyperfiltration will start a self-perpetuating glomerular injury (37,38).

Hyperglycemia is also associated with the development of advanced glycation end products (AGEs), which are believed to play an important role in the pathogenesis of both MA and RP (39,40) and may predict morphologic changes in the kidney (41). Changes in the level of AGEs is seen early, within 2 years of diabetes, and are correlated to the glycemic level (HbA_{1c}) (42,43). The hypothesis of a “long-time glycemic memory” may be supported by findings in a follow-up study from the DCCT, where the reduction in risk of complications from intensive insulin therapy persists despite increasing hyperglycemia (44), perhaps also mediated via AGE levels (42).

Previously, male sex, smoking, and low birth weight have been shown to be risk factors for the development of nephropathy and retinopathy (6,45–49). However, in this rather small retrospective study with a limited follow-up time, we could not confirm these associations; these factors were all controlled for in the analyses on the effect of glycemic level (HbA_{1c}).

Some patients (23.5%) with MA did not have concomitant RP, and this is in

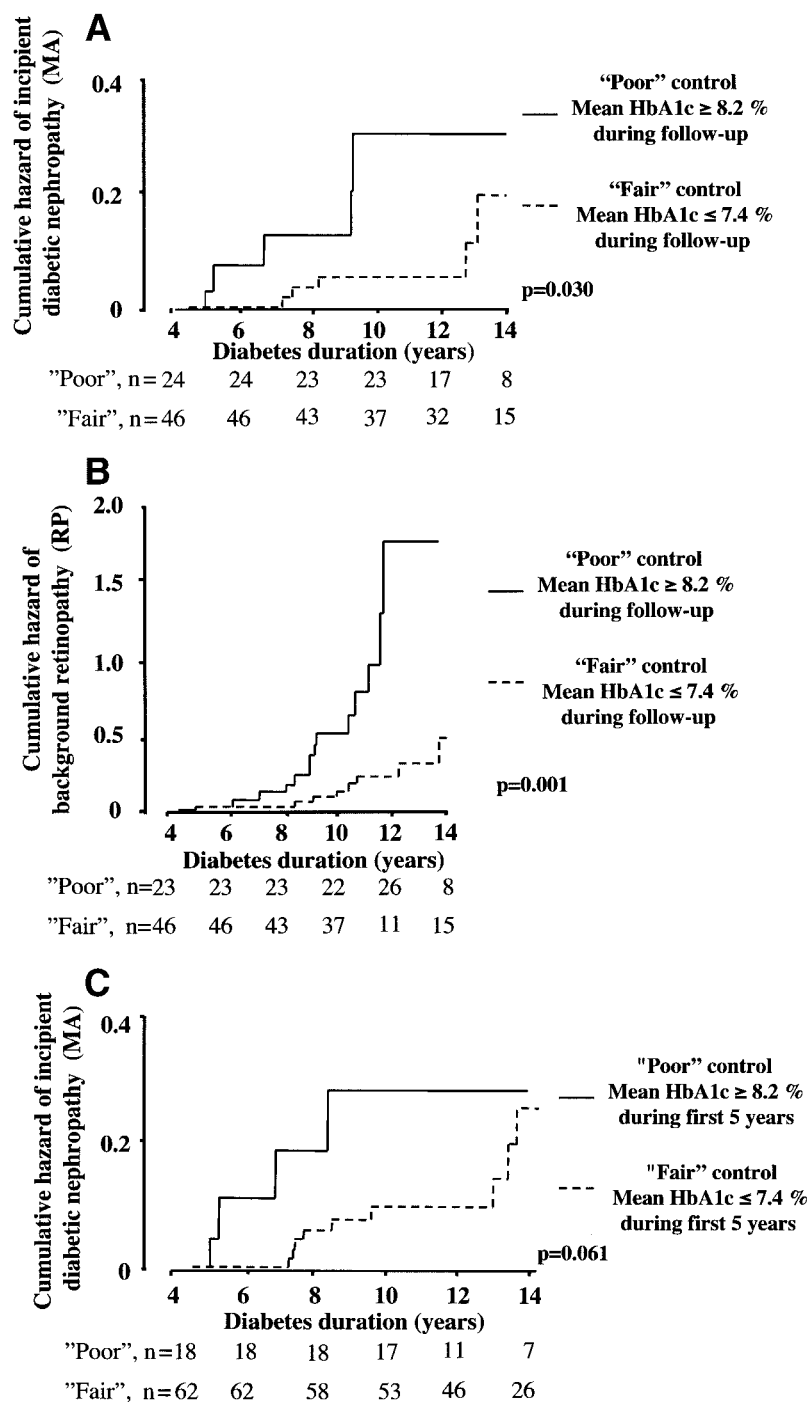


Figure 2—Cumulative hazard rates (Cox regression) of developing MA (A) and RP (B) as functions of “poor” (HbA_{1c} ≥8.2%) or “fair” (HbA_{1c} ≤7.4%) glycemic control to onset of complication or during 14 years of follow-up (75th percentile of diabetes duration). MA as functions of “poor” (HbA_{1c} ≥8.2%) or “fair” (HbA_{1c} ≤7.4%) glycemic control during the first 5 years of diabetes (early) (C). n, number of patients in each group followed to the indicated time.

accordance with some previous studies (8). These findings are important from a clinical point of view, as a lack of RP does not exclude MA.

In this study, we also found differ-

ences in the fall in HbA_{1c} levels between patients developing MA and those developing RP. We speculate that the diagnosis of MA makes the diabetologist and the patient more active to control glycemia

than the diagnosis of RP. This may perhaps be due to the fact that screening for microalbuminuria is done in the same department, and the result is present at patient visits in contrast to retinal screening, which is done in a different department and the report arrives to the diabetologist between patient visits.

Age at onset of diabetes was a weak but statistically significant risk factor for RP after adjusting for glycemic control and duration. Moreover, diagnosis of diabetes before the age of 5 years significantly prolonged the time to occurrence of RP, compared with the age-groups 5–11 and >11 years, indicating a protective effect of prepubertal duration. This could not be found for MA, but we need to bear in mind that the number of patients who developed microalbuminuria in our study was small. The results in other studies have been not been consistent; some showed a small impact of prepubertal diabetes duration (50–52) on the development of complications and others failed to do so (10,12,21,53). The present study and other studies (15,54) indicate that children with an onset of diabetes before the age of 5 years may have a prolonged time to development of microvascular complications. Thus, the youngest age-groups, who are most sensitive to hypoglycemia with regard to risk of persistent brain damage, may have a relative protection during childhood or a longer time to development of complications. However, as the blood glucose level, both early and late, is a powerful predictor for future development of microvascular complications, one must continue to encourage the pediatric diabetologist to optimize the glucose level but at the same time avoid hypoglycemic episodes from the diagnosis of diabetes, regardless of age in these children.

When interpreting these results, it must be kept in mind that our study and others have a limited period of follow-up and that the estimated microalbuminuria is a surrogate marker for diabetic nephropathy. In our study, ~40% of the patients diagnosed with MA normalized their microalbuminuria spontaneously during follow-up without treatment with ACE inhibitors. This is comparable with studies where determinants of regression and progression of microalbuminuria have been studied (16,55).

In conclusion, poor early glycemic control, already during the first 5 years of

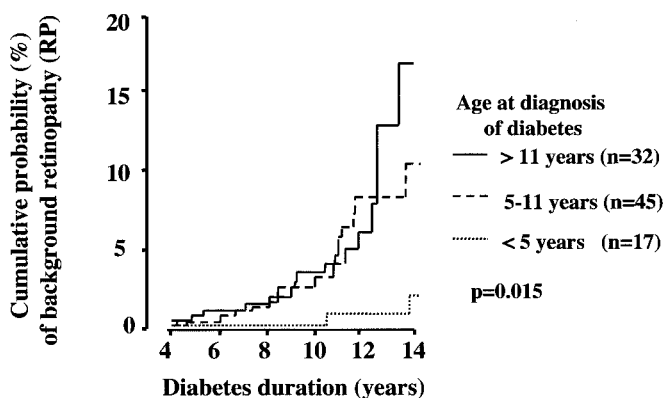


Figure 3—Cumulative probability (Kaplan-Meier) of developing RP for years of diabetes duration. Groups are represented by age at diagnosis: <5, 5–11, and >11 years. n, number of patients in each age-at-onset group.

diabetes duration, was associated with development of detectable microvascular complications in >50% of young patients with type 1 diabetes with ~12 years duration of type 1 diabetes. Onset of diabetes before the age of 5 years may, however, be associated with delay in the occurrence of complications. The clinical dilemma for the pediatric diabetologist to use intensified insulin treatments to decrease hyperglycemia without increasing the frequency of severe hypoglycemic episodes is still an important challenge for the future.

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