Impact of Age of Onset, Puberty, and Glycemic Control Followed From Diagnosis on Incidence of Retinopathy in Type 1 Diabetes: The VISS Study

Maria Nordwall,[1,2] Mats Fredriksson,[3,4] Johnny Ludvigsson,[1,5] and Hans J. Arnqvist[6]

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OBJECTIVE

To evaluate sex, age at diabetes onset, puberty, and HbA_{1c}, with subjects followed from diabetes diagnosis and during different time periods, as risk factors for developing diabetic simplex and proliferative retinopathy.

RESEARCH DESIGN AND METHODS

In a population-based observational study, HbA_{1c} for 451 patients diagnosed with diabetes before 35 years of age during 1983–1987 in southeast Sweden was followed for up to 18–24 years from diagnosis. Long-term mean weighted HbA_{1c} ($wHbA_{1c}$) was calculated. Retinopathy was evaluated by fundus photography and analyzed in relation to $wHbA_{1c}$ levels.

RESULTS

Lower $wHbA_{1c}$, diabetes onset ≤5 years of age, and diabetes onset before puberty, but not sex, were associated with longer time to appearance of simplex retinopathy. Proliferative retinopathy was associated only with $wHbA_{1c}$. The time to first appearance of any retinopathy decreased with increasing $wHbA_{1c}$. Lower $wHbA_{1c}$ after ≤5 years' diabetes duration was associated with later onset of simplex retinopathy but not proliferative retinopathy. With time, most patients developed simplex retinopathy, except for those of the category $wHbA_{1c}$ ≤50 mmol/mol (6.7%), for which 20 of 36 patients were without any retinopathy at the end of the follow-up in contrast to none of 49 with $wHbA_{1c}$ >80 mmol/mol (9.5%).

CONCLUSIONS

Onset at ≤5 years of age and lower $wHbA_{1c}$ the first 5 years after diagnosis are associated with longer duration before development of simplex retinopathy. There is a strong positive association between long-term mean HbA_{1c} measured from diagnosis and up to 20 years and appearance of both simplex and proliferative retinopathy.

HbA_{1c} was introduced in diabetes care in the early 1980s as a measure of average glycemia during the prior 6–10 weeks (1). Many studies have demonstrated that the level of HbA_{1c} is closely related to development of diabetes complications in type 1 diabetes (2–5). Besides glycemic control, diabetes duration is a strong risk factor for diabetic retinopathy, but there is evidence that the effect of duration is not uniform,

[1]Division of Paediatrics, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Östergötland, Sweden
[2]Vrinnevi Hospital, Norrköping, Östergötland, Sweden
[3]Division of Occupational and Environmental Medicine, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Östergötland, Sweden
[4]Forum Östergötland, Linköping University, Linköping, Östergötland, Sweden
[5]Division of Paediatrics, Department of Clinical and Experimental Medicine, Crown Princess Victoria Children's Hospital, Linköping University, Linköping, Östergötland, Sweden
[6]Departments of Endocrinology and Clinical and Experimental Medicine, Linköping University, Linköping, Östergötland, Sweden

Corresponding author: Hans J. Arnqvist, hans.arnqvist@liu.se

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being modified by age at diabetes onset (6,7) and puberty (8–10). Duration of diabetes before puberty seems to prolong the time to occurrence of both nephropathy and retinopathy (11). The protective effect of younger age at diagnosis tends to disappear with time (12). Some studies have shown a greater risk for complications in patients with diabetes onset at younger ages (13). Poor glycemic control during the first 5 years after diagnosis has also been suggested to be an independent risk factor for retinopathy (14). A negative influence of puberty on the appearance of diabetic retinopathy may be due to the combination of hormonal changes and the very poor glycemic control often seen in adolescents (15). In a recent report (the VISS Study [Vascular Diabetic Complications in Southeast Sweden]) on development of severe retinopathy (defined as laser-treated proliferative retinopathy) and nephropathy (defined as persistent macroalbuminuria) with HbA_{1c} followed from diagnosis, we found that after a diabetes duration of 20 years no patient having a long-term mean weighted HbA_{1c} ($wHbA_{1c}$) $<$7.6% (60 mmol/mol) developed any of these complications (16).

Our aim was to analyze the impact of HbA_{1c}, followed from diagnosis and during different time periods; relation to puberty; age at diagnosis; and sex as risk factors for developing diabetic simplex and proliferative retinopathy.

RESEARCH DESIGN AND METHODS

Patients

An unselected population comprising all 451 patients diagnosed with type 1 diabetes before the age of 35 years from 1 January 1983 to 31 December 1987 in the southeast hospital region in Sweden with just over 900,000 inhabitants was studied. The patients were identified with local registers at each clinic. That all patients were included in this unselected population was validated with help of incidence registers, the Swedish Childhood Diabetes Registry (17) and the Diabetes Incidence Study in Sweden (DISS) registry (18).

Data were retrospectively collected in the patients' journals or by a questionnaire to their physicians. Most of the patients were followed until 2005–2008. Mean (SD) duration at follow-up was 22.1 (2.0) years. For 17 patients (4%), it was not possible to track data for the whole time period until follow-up. Of these 17 patients, 11 were deceased and 6 had moved abroad. The period of puberty was defined as 10.0–14.9 years of age for girls and 12.0–16.9 years for boys (Swedish growth charts, 2002 [19]).

The Research Ethics Committee of the Faculty of Health Sciences, Linköping University, approved the study.

Retinopathy

Retinal screening using color fundus photography was planned every other year for each patient from the onset of diabetes and from 10 years of age. Three standard photographs were taken, after pupil dilation, of each eye: nasal to the optic nerve, the optic nerve and macula, and temporal to the macula. The prevalence of retinopathy was calculated based on reevaluation of fundus photos taken between 2005 and 2008. If no photo was available during this period, the last photo, closest to these dates, was selected. The duration of diabetes at the date of photography was mean (SD) 20.8 (2.9) years. The date of the first laser treatment was collected from clinical records. Photographs or reliable data concerning previous laser therapy for proliferative retinopathy or maculopathy were available for 431 (96%) patients. Eleven patients had died, 6 patients had moved abroad, and 3 patients had not participated in screening. Two ophthalmologists evaluated the photographs independently. The photographs were graded according to the modified Airlie House protocol. For each eye and type of retinopathic lesion, subscales grading the severity of the lesion were applied and then grouped according to the worst eye into four classes: normal, slight simplex, moderate simplex, and proliferative retinopathy or maculopathy or previous laser therapy (20). If the grading was dissimilar, the ophthalmologists reevaluated the photos and then together decided the grading.

The incidence of simplex retinopathy was examined by collecting data from the records from the clinics of ophthalmology in the region. The first recording of any diabetes-related retinal lesion, commonly microaneurysms, was defined as onset of retinopathy. It was not possible to collect these data for patients who had moved out of the region, which is why only 281 (62%) patients participated in this part of the study.

The incidence of proliferative retinopathy, defined as the date of first laser treatment, was also calculated. Here it was possible to get data from 431 of 451 (96%) of the population.

HbA_{1c} Measurement

HbA_{1c} was measured regularly at the clinical visits, two to four times per year, and analyzed by local hospital laboratories. At the start of the study in January 1983, HbA_{1c} was analyzed by Isolab minicolumns (Fast Hb Test System; Isolab Inc., Akron, OH) at the four central laboratories. This was replaced during 1984–1987 by high-performance liquid chromatography methods measuring HbA_{1c} with high precision. The analyzing laboratories calculated intermethod calibrations and conversion factors when the methods were changed. From June 1994, hospital laboratories were participating in an interlaboratory quality program (Equalis, Uppsala, Sweden), where all laboratories analyzed two samples per month. In 1997, a nationwide standardization was introduced, and repeated comparisons were made with National Glycohemoglobin Standardization Program (NGSP) values, which showed the Swedish values to be 1.1% lower than NGSP values (21). The same was demonstrated in a study comparing HbA_{1c} measured in 1994 at the Linköping Hospital laboratory with results from the Diabetes Control and Complications Trial (DCCT) laboratory (22). All values are converted by formulas to the new International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference values (23). The corresponding NGSP values are also stated, making it possible to compare the results with previous studies. The conversion formula is HbA_{1c} (NGSP) (%) = 0.09153 HbA_{1c} (IFCC) (mmol/mol) + 2.153. The normal range is 27–42 mmol/mol (IFCC) corresponding to 4.6–6.0% (NGSP). For many of the patients who moved, it was possible to obtain their HbA_{1c} values from their physicians, and conversions factors to the Equalis reference method was done by the analyzing laboratory. However, 90% of the HbA_{1c} values come from laboratories in the catchment area. As a measure of long-term glycemic control, all HbA_{1c} values, from diabetes diagnosis and until the date for first detection of

retinopathy or year of laser therapy or time of last follow-up, were used for the calculations. Mean $wHbA_{1c}$ was calculated using the area under the graph of time versus HbA_{1c}, divided by the total follow-up time for each patient, thereby compensating for the occasionally irregular intervals between measurements (6,24).

$wHbA_{1c}$ was calculated for the whole follow-up period as well as for the periods before, during, and after puberty. $wHbA_{1c}$ for the periods during the first 5 years after diagnosis and >5 years after diagnosis was also calculated.

Statistical Analysis

For statistical analysis, $wHbA_{1c}$ was divided into five different classes. For some analyses, it was necessary to combine categories because of the absence of readings in the lowest categories.

Differences between groups were tested with *t* test, ANOVA, or general linear model (GLM) repeated measures with Bonferroni post hoc test.

Life table analysis with Wilcoxon (Gehan) log-rank test was used for analysis of incidence of any retinopathy and laser-treated proliferative retinopathy.

Cox proportional hazards regression model was used to analyze the relative contribution of covariates to the risk of developing simplex retinopathy and laser-treated proliferative retinopathy. Variables included in the model were age at diabetes diagnosis; onset before, during, and after puberty; sex; and mean $wHbA_{1c}$ during the whole follow-up and during different periods.

Logistic regression was used to analyze the prevalence of retinopathy at the end of the follow-up period. Sex, age at onset, and $wHbA_{1c}$ during different time periods were included in the models.

Data are shown as mean (SD) unless otherwise stated. The significance level was set as $P < 0.05$. SPSS, version 21, was used for the analyses.

RESULTS

Patient Population

The number of patients diagnosed before, during, and after puberty and $wHbA_{1c}$ for the follow-up period of mean (SD) 22.1 (2.0) years are shown in Table 1. There was no difference in $wHbA_{1c}$ between patients diagnosed before and during puberty, whereas $wHbA_{1c}$ was lower in those diagnosed

Table 1—Long-term mean $wHbA_{1c}$ during whole follow-up of 18–24 years in an unselected population with type 1 diabetes with onset before, during, or after puberty

	Subgroup evaluated for incidence of simplex retinopathy				All patients evaluated for incidence of proliferative retinopathy			
	All	Female	Male	*P**	All	Female	Male	*P*
Diabetes onset								
Before puberty	68 (12) [8.4 (1.1)], 104	71 (10) [8.6 (0.9)], 40	67 (13) [8.3 (1.2)], 64	0.04	68 (12) [8.4 (1.1)], 160†	71 (10) [8.6 (0.9)], 68‡	66 (13) [8.2 (1.2)], 92	0.02
During puberty	69 (16) [8.5 (1.5)], 51	76 (15) [9.1 (1.4)], 22	64 (15) [8.0 (1.4)], 29	0.01	68 (13) [8.4 (1.2)], 88§	72 (15) [8.7 (1.4)], 37‡	65 (10) [8.1 (0.9)], 51	0.01
After puberty	64 (15) [8.0 (1.4)], 126	68 (18) [8.4 (1.7)], 53	62 (12) [7.8 (1.1)], 73	0.06	64 (13) [8.0 (1.2)], 183	63 (14) [7.9 (1.3)], 81	64 (12) [8.0 (1.2)], 102	0.47
Age at onset (years)								
0–4.9	67 (10) [8.3 (0.9)], 32	68 (8) [8.4 (0.7)], 14	65 (12) [8.1 (1.1)], 18	0.38	67 (10) [8.3 (0.9)], 51	68 (8) [8.4 (0.7)], 25	67 (12) [8.3 (1.1)], 26	0.61
5–9.9	69 (13) [8.5 (1.2)], 64	73 (11) [8.8 (1.0)], 26	67 (14) [8.3 (1.3)], 38	0.07	69 (12) [8.5 (1.1)], 94	72 (10) [8.7 (0.9)], 43‖	66 (13) [8.2 (1.2)], 51	0.02
10–14.9	71 (16) [8.6 (1.5)], 50¶	76 (15) [9.1 (1.4)], 22¶	67 (15) [8.3 (1.4)], 28	0.05	68 (14) [8.4 (1.3)], 90	71 (16) [8.6 (1.5)], 39‖	65 (11) [8.1 (1.0)], 51	0.04
15–19.9	64 (16) [8.0 (1.5)], 32	63 (19) [7.9 (1.7)], 13	65 (15) [8.1 (1.4)], 19	0.75	63 (13) [7.9 (1.2)], 56	60 (11) [7.6 (1.0)], 24	66 (13) [8.2 (1.2)], 32	0.05
20–24.9	60 (15) [7.6 (1.4)], 34	59 (19) [7.5 (1.7)], 12	61 (11) [7.7 (1.0)], 22	0.64	63 (12) [7.9 (1.1)], 47	61 (15) [7.7 (1.4)], 18	64 (9) [8.0 (0.8)], 29	0.52
25–29.9	67 (17) [8.3 (1.6)], 37	74 (18) [8.9 (1.7)], 18	60 (12) [7.6 (1.1)], 19	0.01	63 (13) [7.9 (1.1)], 51	65 (15) [8.1 (1.4)], 24	62 (11) [7.8 (1.0)], 26	0.45
30–34	65 (10) [8.1 (0.9)], 32	73 (10) [8.8 (0.9)], 10	62 (9) [7.8 (0.8)], 22	<0.01	66 (12) [8.2 (1.1)], 43	69 (11) [8.5 (1.0)], 13	65 (12) [8.1 (1.1)], 30	0.310
Total	67 (14) [8.3 (1.3)], 281	70 (15) [8.6 (1.4)], 115	64 (13) [8.0 (1.2)], 166	<0.001	66 (12) [8.2 (1.1)], 431	68 (13) [8.4 (1.2)], 186	65 (12) [8.1 (1.1)], 245	0.04

Puberty defined as age 10.0–14.9 years for girls and 12.0–16.9 years for boys. Mean (SD) $wHbA_{1c}$ data are expressed as mmol/mol [%], number of individuals. *P value for the difference between female and male, *t* test; †$P = 0.002$ compared with after puberty; ‡$P = 0.001$ compared with after puberty; §$P = 0.021$ compared with after puberty; ‖$P < 0.02$ compared with age 15–19.9 years; ¶$P < 0.05$ compared with age 20–24.9 years. ANOVA with Bonferroni post hoc test.

after puberty. When separated according to sex, female patients with onset after puberty had lower $wHbA_{1c}$ in comparison with those with onset before and during puberty, whereas no significant differences were found for males. Both in the whole group and in the subgroup evaluated for incidence of simplex retinopathy, $wHbA_{1c}$ was higher in females, except in the group diagnosed after puberty (Table 1).

To test the influence of age at onset on development of retinopathy, we categorized age at onset into 5-year intervals (Table 1). In the subgroup evaluated for incidence of simplex, the highest $wHbA_{1c}$ values were found for females with age at onset 10–14.9 years, and among all patients the highest values were found for females with age at onset 5–9.9 and 10–14.9 years.

$wHbA_{1c}$ was also calculated for different time periods, i.e., ≤5 years after onset, >5 years after onset, and before, during, and after puberty (Table 2). $wHbA_{1c}$ was lower during the first 5 years compared with $wHbA_{1c}$ during the following years. Females had higher $wHbA_{1c}$ than males after 5 years' diabetes duration. $wHbA_{1c}$ before puberty was lower than during and after puberty. Females had higher $wHbA_{1c}$ than males after puberty (Table 2).

Incidence of Simplex Retinopathy

The incidence of first appearance of simplex retinopathy was studied in the subgroup of patients who had not moved out from our hospital region (Table 1). The level of $wHbA_{1c}$ was categorized into five levels: ≤6.7% (50 mmol/mol), 6.8–7.6% (51–60 mmol/mol), 7.7–8.6% (61–70 mmol/mol), 8.7–9.5% (71–80 mmol/mol), and >9.5% (80 mmol/mol). As can be seen from Fig. 1*A*, the first appearance of retinopathy occurred earlier with increasing HbA_{1c} categories. This difference was most obvious after ∼15 years' duration. With time, most patients developed simplex retinopathy and the difference between the HbA_{1c} categories regarding simplex retinopathy decreased. In evaluations at the end of the follow-up period, simplex retinopathy had regressed to no retinopathy in 18 patients. This group had a mean (SD) $wHbA_{1c}$ value of 7.0% (0.7%) (53 [8] mmol/mol) compared with 8.6% (1.3%) (70 [14] mmol/mol) in the group who did not regress ($P < 0.001$).

Table 2—Long-term $wHbA_{1c}$ calculated for different time periods, i.e., ≤5 years after onset, >5 years after onset, and also before, during, and after puberty

	Subgroup evaluated for incidence of simplex retinopathy				All patients evaluated for incidence of proliferative retinopathy			
	All	Female	Male	*P**	All	Female	Male	*P**
$wHbA_{1c}$ after ≤5 years' duration	61 (15) [7.7 (1.4)], 265	64 (17) [8.0 (1.6)], 107	59 (14) [7.5 (1.3)], (158)	0.05	61 (16) [7.7 (1.5)], 427	63 (16) [7.9 (1.5)], 185	60 (15) [7.6 (1.4)], 242	0.08
$wHbA_{1c}$ after >5 years' duration	71 (16) [8.6 (1.5)]	75 (17) [9.0 (1.6)]	68 (14) [8.4 (1.3)]	0.01	68 (13) [8.4 (1.2)]	70 (14) [8.6 (1.3)]	67 (12) [8.3 (1.1)]	0.04
P†	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
$wHbA_{1c}$ before puberty	60 (14) [7.6 (1.3)], 87‡	60 (13) [7.6 (1.2)], 34‡	61 (14) [7.7 (1.3)], 53‡	0.88	60 (13) [7.6 (1.2)], 143§	60 (11) [7.6 (1.0)], 56§	60 (14) [7.6 (1.3)], 87§	0.93
$wHbA_{1c}$ during puberty	70 (14) [8.6 (1.3)]‖	70 (11) [8.6 (1.0)]¶	69 (16) [8.5 (1.5)]	0.86	71 (14) [8.6 (1.3)]	72 (12) [8.7 (1.1)]	70 (15) [8.6 (1.4)]	0.50
$wHbA_{1c}$ after puberty	73 (16) [8.8 (1.5)]	79 (16) [9.4 (1.5)]	70 (15) [8.6 (1.4)]	0.01	71 (14) [8.6 (1.3)]	74 (11) [89 (1.0)]	68 (14) [8.4 (1.3)]	<0.01
P#	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	

Mean (SD) $wHbA_{1c}$ data expressed as mmol/mol [%], number of individuals. **P* value for the difference between female and male, *t* test; †*P* value for the difference between $wHbA_{1c}$ ≤5 years' duration and >5 years' duration, paired *t* test; ‡$P < 0.001$ compared with during and after puberty, GLM; §$P < 0.001$ compared with during and after puberty, GLM; ‖$P = 0.033$ compared with after puberty; ¶$P = 0.01$ compared with after puberty, GLM; #*P* value for the difference between $wHbA_{1c}$ before, during, and after puberty, GLM.

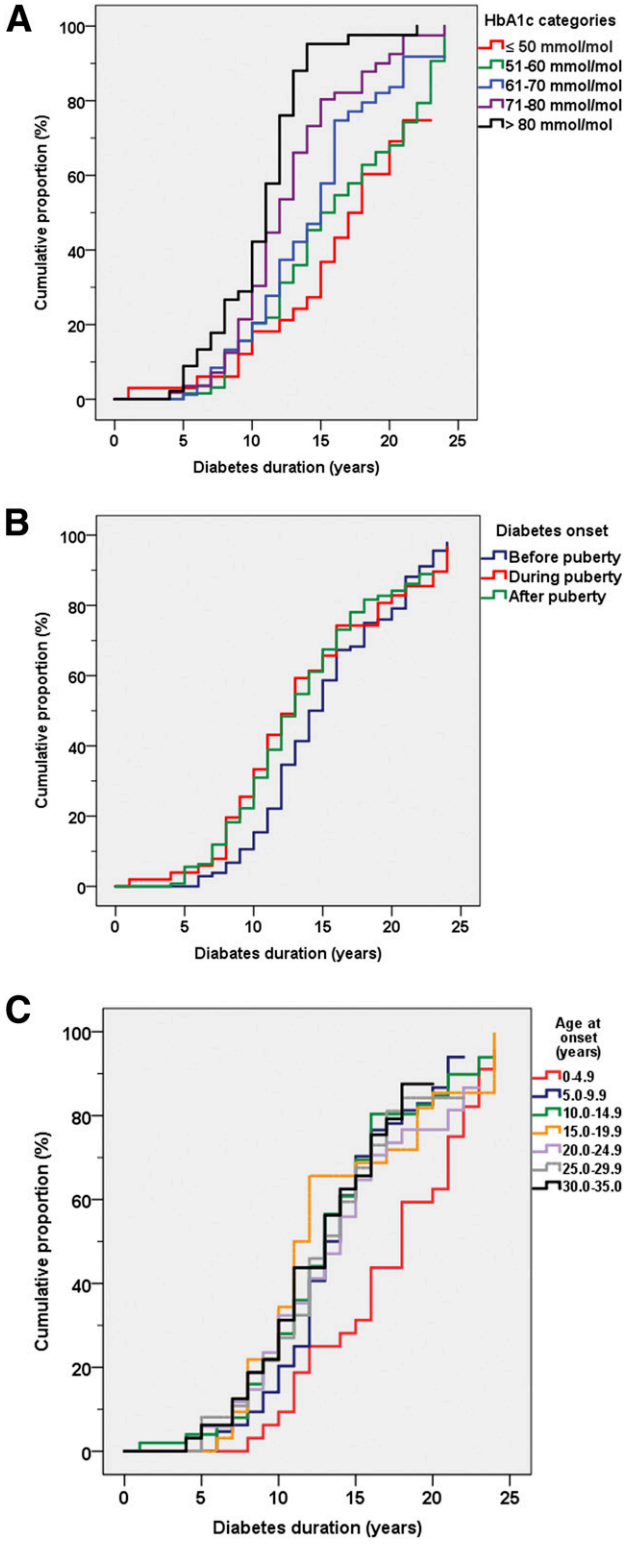

Figure 1—*A*: Incidence of simplex retinopathy in different long-term wHbA$_{1c}$ categories in an unselected population with type 1 diabetes followed for 18–24 years. Overall significance $P < 0.001$. $P = 0.02$ for 7.7–8.6% (61–70 mmol/mol) and $P < 0.01$ for 8.7–9.5% (71–80 mmol/mol) and for >9.5% (80 mmol/mol) in comparison with <50 mmol/mol. *B*: Incidence of simplex retinopathy in relation to onset before, during, and after puberty. Overall significance $P = 0.03$, before and during puberty $P = 0.04$, and before and after puberty $P = 0.01$. Puberty defined as age 10.4–14.9 years for girls and 12.0–16.9 years for boys. *C*: Incidence of simplex retinopathy in relation to age of onset in an unselected population of type 1 diabetes followed for 18–24 years. Overall significance $P = 0.024$. $P = 0.003$–0.022 for 0–4 years age-group in comparison with older age-groups, while there were no significant differences between the other age-groups.

Patients diagnosed with diabetes before puberty had longer time to development of simplex retinopathy than those diagnosed during or after puberty, as shown in Fig. 1*B*. Figure 1*C* shows that simplex retinopathy appeared significantly later only in the group with diabetes onset before 5 years of age.

We performed a univariate Cox proportional hazards regression analysis of factors associated with development of first sign of retinopathy using a model (model A) with sex; diabetes diagnosis before, during, and after puberty; and wHbA$_{1c}$. Besides wHbA$_{1c}$, onset before puberty, but not sex, was significantly associated with later development of first sign of retinopathy (Table 3).

In univariate Cox proportional hazard regression analysis, including sex, age at onset categorized into 5-year intervals, and wHbA$_{1c}$, we found that, in addition to wHbA$_{1c}$, onset before 5 years of age was associated with delayed onset of simplex retinopathy ($P = 0.001$) (Table 3 [model B]). If wHbA$_{1c}$ was divided into wHbA$_{1c}$ after ≤5 years of diabetes duration and wHbA$_{1c}$ after >5 years of diabetes duration, both time periods were significantly associated with development of simplex retinopathy (Table 3 [model C]). When wHbA$_{1c}$ was divided according to the periods before, during, and after puberty, age of onset and wHbA$_{1c}$ after puberty were associated with simplex retinopathy (Table 3 [model D]). It should be noted that in this model only patients diagnosed before puberty are included.

Incidence of Proliferative Retinopathy

In univariate Cox proportional hazards regression analysis including wHbA$_{1c}$, onset in relation to puberty, and sex (Table 3 [model A]), only wHbA$_{1c}$ had a major impact ($P < 0.001$). If puberty was replaced by age at onset in the Cox regression analysis, a similar result was obtained and only wHbA$_{1c}$ was associated with the risk of proliferative retinopathy (Table 3 [model B]). If wHbA$_{1c}$ was divided into different time periods, wHbA$_{1c}$ after 5 years' diabetes duration and wHbA$_{1c}$ after puberty were significantly associated with proliferative retinopathy (Table 3 [models C and D]). In model D, age of onset was significantly ($P = 0.04$) associated with proliferative retinopathy.

Table 3—Cox regression models of risk factors for simplex and proliferative retinopathy

		Simplex retinopathy			Proliferative retinopathy		
Model	Risk factor	*P*	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI
A	Sex (women/men)	0.55	0.92	0.71–1.20	0.84	0.95	0.55–1.62
	Onset before puberty	<0.001	0.57	0.43–0.77	0.92	1.03	0.57–1.89
	Onset during puberty	0.38	0.85	0.60–1.22	0.47	1.28	0.65–2.50
	Onset after puberty		Reference			Reference	
	$wHbA_{1c}$	<0.001	1.05	1.03–1.06	<0.001	1.10	1.08–1.12
B	Sex (women/men)	0.73	0.95	0.74–1.24	0.89	0.96	0.56–1.65
	Onset 0.0–4.9 years	0.001	0.38	0.22–0.66	0.69	0.77	0.22–2.77
	Onset 5.0–9.9 years	0.08	0.66	0.42–1.06	0.92	1.06	0.35–3.21
	Onset 10.0–14.9 years	0.50	0.85	0.52–1.38	0.64	1.30	0.43–3.91
	Onset 15.0–19.9 years	0.94	0.98	0.57–1.67	0.98	0.99	0.28–3.52
	Onset 20.0–24.9 years	0.50	0.83	0.49–1.42	0.83	0.86	0.23–3.26
	Onset 25.0–29.9 years	0.96	0.99	0.59–1.66	0.58	0.69	0.18–2.61
	Onset 30.0–34.9 years		Reference			Reference	
	$wHbA_{1c}$	<0.001	1.05	1.04–1.06	<0.001	1.10	1.08–1.12
C	Sex (women/men)	0.57	0.93	0.71–1.21	0.95	1.02	0.60–1.74
	Age at onset	<0.001	1.03	1.01–1.04	0.48	1.01	0.98–1.04
	$wHbA_{1c}$ ≤5 years	0.03	1.01	1.00–1.02	0.31	0.99	0.97–1.01
	$wHbA_{1c}$ >5 years	<0.001	1.04	1.03–1.05	<0.001	1.12	1.09–1.14
D	Sex (women/men)	0.74	0.92	0.56–1.51	0.06	2.54	0.98–6.56
	Age at onset	<0.001	1.24	1.14–1.36	0.04	1.22	1.01–1.47
	$wHbA_{1c}$ before puberty	0.69	1.01	0.98–1.03	0.69	0.99	0.95–1.03
	$wHbA_{1c}$ during puberty	0.32	1.01	0.99–1.04	0.68	1.01	0.97–1.05
	$wHbA_{1c}$ after puberty	0.02	1.03	1.01–1.05	<0.001	1.12	1.06–1.18

Prevalence of Retinopathy

At the end of the follow-up only 54 patients (12.5%) had no signs of retinopathy and 145 (33.6%) had slight simplex, 175 (40.5%) moderate simplex, and 57 (13.2%) proliferative retinopathy. There were no cases of maculopathy, and all patients with proliferate retinopathy were laser treated. Twenty of 36 patients with $wHbA_{1c}$ ≤6.7% (50 mmol/mol) were without any retinopathy but none of 49 with $wHbA_{1c}$ >9.5% (80 mmol/mol) were without any retinopathy. In logistic regression analysis of risk factors for simplex and proliferative retinopathy, age at onset and onset before, during, and after puberty were not significant, while $wHbA_{1c}$ for the whole follow-up period was highly significant ($P < 0.001$) (Supplementary Table 1). In model 3 with $wHbA_{1c}$ before, during, and after puberty, which only includes patients with onset before puberty, borderline significance was found for the association of proliferative retinopathy with sex and age of onset, while $wHbA_{1c}$ after puberty was highly significant.

CONCLUSIONS

In this study of diabetic retinopathy, HbA_{1c} was followed continuously for 18–24 years from diagnosis in patients with type 1 diabetes, and to our knowledge this is the only study with HbA_{1c} followed from diagnosis for such a long time. Long-term mean $wHbA_{1c}$ was calculated and related to the appearance of simplex and proliferative retinopathy. The time to the appearance of the first signs of simplex retinopathy was found to be markedly influenced by the level of $wHbA_{1c}$, as was also reported in the primary prevention cohort of DCCT (2) and in other studies (14). However, with time, the majority, but not all, of the patients developed simplex retinopathy—in agreement with a recent report (12). In the evaluation of the level of HbA_{1c} and the risk of retinopathy in DCCT, it was concluded that "over the range HbA_{1c} achieved by DCCT intensive therapy, there does not appear to be a level of glycemia below which the risks of retinopathy progression are eliminated" (25). We can confirm this statement, as even in patients with very well-controlled diabetes, with $wHbA_{1c}$ of ≤6.7% (50 mmol/mol), 44% had developed simplex retinopathy after 20 years. In this context, it should be pointed out that based on evaluation of epidemiological data, the hyperglycemic threshold for diagnosis of diabetes is set at the level where microangiopathy develops (26). Complete avoidance of retinopathy in patients with type 1 diabetes evidently requires a very tight glycemic control, which is very difficult to achieve with the treatment tools available today and is also dangerous because of the risk of severe hypoglycemia (27). Furthermore, simplex retinopathy does not impair vision, in contrast to proliferative retinopathy, which of course should be avoided. We previously reported that in the patients included in this study, proliferative retinopathy did not occur in any patients with a long-term $wHbA_{1c}$ <7.6% (60 mmol/mol) (16).

The role of prepubertal diabetes duration in development of microangiopathy has been a matter of debate, with reports suggesting a range from no or minimal effect (9) to being an additional independent risk factor for proliferative diabetic retinopathy (13). When onset before, during, and after puberty, defined as 10.0–14.9 years for girls and 12.0–16.9 years for boys, was tested in Cox regression adjusted for sex and $wHbA_{1c}$, onset before puberty was associated with later onset for development of simplex retinopathy. When age of onset was introduced in the model, only onset before 5 years of age was associated with later development of simplex retinopathy, in agreement with other reports (11,14). Porta et al.

(12) defined prepubertal age as 0–12 years in males and 0–11 years in females and found that the prevalence of any retinopathy by duration was lower in patients with onset before puberty, but after 20 years' duration the difference disappeared, as in our study. Thus, there is strong evidence that age at onset of diabetes affects the time to develop simplex retinopathy, while it is unclear whether puberty by itself has an effect beside age at onset.

$wHbA_{1c}$ was lower during the first 5 years after diabetes onset than later. This is probably due to persistent endogenous insulin secretion. Most patients go into partial remission after starting insulin treatment (28,29). In Cox regression analysis, $wHbA_{1c}$ both during the first 5 years after diabetes onset and later were associated with the incidence of simplex retinopathy, whereas only $wHbA_{1c}$ in the period after >5 years' duration was associated with proliferative retinopathy. This suggests that $wHbA_{1c}$ during the first years after diabetes onset has less impact on development of proliferative retinopathy. We can only speculate from our study that the explanation may be that the total glycemic load is of greater importance than HbA_{1c} during shorter time periods.

In Cox regression, we found no association between proliferative retinopathy and age at onset or onset in relation to puberty. This contrasts with the EURODIAB Prospective Complications Study, which found an increased risk for patients with onset before puberty (13). In that study, HbA_{1c} was not followed from diagnosis, and age at diagnosis <12 years was defined as before puberty. Beside HbA_{1c}, baseline retinopathy was a strong risk factor and with adjustment for this and urinary albumin excretion, age at diagnosis <12 years was no longer a significant risk factor ($P < 0.08$). In a sample of 1,117 patients with type 1 diabetes, consecutively recruited in the Finnish Diabetic Nephropathy (FinnDiane) Study and divided into age-at-onset groups 0–4, 5–14, and 15–40 years, the age-group 0–4 years had the longest mean duration, 24.3 years (95% CI 22.7–25.9), to development of proliferative retinopathy (30). In a Cox regression model, the highest risk of proliferative retinopathy was observed in the 5–14 years age-group. Also, in that study HbA_{1c} was not followed from diagnosis. As in the FinnDiane Study, in our study there was a positive association of age at onset with proliferative retinopathy in the Cox regression model D with $wHbA_{1c}$ before, during, and after puberty—in which only patients with onset before puberty are included. These data are not quite conclusive but may suggest that age at onset/puberty somehow modifies the long-term risk of proliferative retinopathy. For the ability to draw firm conclusions about the role of age of onset and $wHbA_{1c}$ after ≤5 years in development of proliferative retinopathy, a diabetes duration longer than 18–24 years, as in our study, is needed.

Strength and Weakness

The strength of our study is that we have followed HbA_{1c} in an unselected population of patients with type 1 diabetes from diabetes onset and managed to follow a large proportion of the whole cohort for >20 years. The study started in the early 1980s, when HbA_{1c} was introduced in diabetes care, which has given us the opportunity to follow HbA_{1c} since diabetes diagnosis. In the calculations, we could adjust for long-term HbA_{1c} during the whole follow-up and during different time periods, which could perhaps explain the difference of our results from those of many other studies, where HbA_{1c} is only analyzed during limited periods. Still, there is a risk of type II errors where we have found no significant associations. The age of the patients at inclusion varied from 0 to 35 years, which makes the study suitable for reviewing the effect of age of onset and puberty. A weakness is that like most other studies, we defined puberty by age range (12,14) and not by clinical investigation. Most of the patients developed simplex retinopathy during the duration of the study, which is favorable for assessment of risk factors. The mean duration for development of proliferative retinopathy is >20 years, which is why the observation time in our study may be too short, or the numbers of cases of proliferative retinopathy too few, to fully assess risk factors for proliferative retinopathy (30).

In clinical practice, it is of great importance to find the balance between the risk of potentially dangerous hypoglycemic events and quality of life and the risk of severe microvascular complications to be able to recommend an evidence-based optimal level of HbA_{1c} both in the short-term and in the long-term. The observation that $wHbA_{1c}$ before and during puberty did not influence the prevalence of proliferative retinopathy at 20 years' diabetes duration is of clinical importance in the setting of targets for glycemic control in young children for whom severe hypoglycemia might be especially dangerous.

Simplex retinopathy is not sight threatening, even if advanced simplex retinopathy is a risk factor for proliferative retinopathy (13). However, simplex retinopathy may regress, and in our study simplex retinopathy regressed in a group of patients with mean $wHbA_{1c}$ 7.0% (SD 0.7%) (53 [8] mmol/mol). Proliferative retinopathy is clinically more relevant and should be avoided. We previously showed that the threshold for proliferative retinopathy is higher than for simplex retinopathy (28). Proliferative retinopathy did not occur in this material in patients with $wHbA_{1c}$ <7.6% (60 mmol/mol), which indicates what should be an important goal for glycemic control. This is in close agreement with the position statement for type 1 diabetes in children and adolescents recently issued by the American Diabetes Association recommending an HbA_{1c} target of <7.5% (58 mmol/mol) (31).

In summary, after 20 years of diabetes duration, there is a strong positive association between long-term mean $wHbA_{1c}$ followed from diagnosis and appearance of both simplex and proliferative retinopathy. Diabetes onset at <5 years of age and lower $wHbA_{1c}$ the first 5 years after diagnosis are associated with longer duration before development of simplex retinopathy but not proliferative retinopathy. Proliferative retinopathy does not appear in patients with $wHbA_{1c}$ <7.6% (60 mmol/mol).

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Author Contributions. M.N. and H.J.A. designed the study, performed the literature research, performed the statistical analysis, interpreted data, and wrote the first draft of the manuscript. M.F. performed the statistical analysis and interpreted data. J.L. designed the study, performed the literature research, and interpreted data. M.N., M.F., J.L., and H.J.A. reviewed and approved the final version of the manuscript. H.J.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix

Clinics participating in the VISS Study Group. Region Jönköpings län, Johan Blomgren (Department of Internal Medicine, Höglandsjukhuset, Eksjö, Sweden), Oskar Lindholm (Department of Internal Medicine, Ryhovs sjukhus, Jönköping, Sweden), Karen Wahlin (Department of Internal Medicine, Värnamo sjukhus, Värnamo, Sweden), and Karin Åkesson (Department of Paediatrics, Ryhovs sjukhus, Jönköping, Sweden); Landstinget i Kalmar län, Marianne Fagerberg (Department of Internal Medicine, Kalmar sjukhus, Kalmar, Sweden), Ulrik Mathiesen (Department of Internal Medicine, Oskarshamns sjukhus, Oskarshamn, Sweden), Marika Berg (Department of Internal Medicine, Västerviks sjukhus, Västervik, Sweden), Göran Lundström (Department of Paediatrics, Kalmar sjukhus, Kalmar, Sweden), and Jan Åke Hammersjö (Department of Paediatrics, Västerviks sjukhus, Västervik, Sweden); Region Östergötland, Ulf Rosenqvist (Department of Internal Medicine, Motala Lasarett, Motala, Sweden) and Anna-Maria Ottoson (Department of Internal Medicine, Vrinnevisjukhuset, Norrköping, Sweden).

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