The Incidence of Retinopathy 10 Years After Diagnosis in Young Adult People With Diabetes

Results from the nationwide population-based Diabetes Incidence Study in Sweden (DISS)

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OBJECTIVE — To estimate the prevalence and severity of diabetic retinopathy (DR) 10 years after diagnosis in a nationwide population-based cohort study of young adult diabetic patients in Sweden.

RESEARCH DESIGN AND METHODS — The Diabetes Incidence Study in Sweden (DISS) aims to register all incident cases of diabetes aged 15–34 years in Sweden. In 1987–1988, 806 cases were reported, and 627 (78%) of them were followed up with regard to retinopathy 8–10 years later. The assessment was based on retinal photographs in most cases (86%).

RESULTS — Ten years after diagnosis, retinopathy was found in 247 patients (39%). The retinopathy was mild in 206 (33%), whereas 30 (4.8%) patients had moderate nonproliferative DR (NPDR) and 11 (1.8%) had proliferative DR (PDR). Patients with retinopathy had worse glycemic control during the years than patients without (HbA_{1c} 8.1 ± 1.5% and 6.8 ± 1.2%, respectively; $P < 0.001$). In a Cox regression analysis, time to retinopathy was related to high HbA_{1c} ($P < 0.001$) and high BMI ($P = 0.001$). Patients with type 2 diabetes had an increased prevalence of severe retinopathy (NPDR or PDR) compared with those with type 1 diabetes (14 of 93 [15%] versus no or mild 24 of 471 [5%], respectively; $P < 0.001$).

CONCLUSIONS — Despite modern diabetes management, 39% of young adult diabetic patients developed retinopathy within the first 10 years of the disease. Nevertheless, compared with the prevalence of retinopathy (63%), after a similar duration of diabetes before the Diabetes Control and Complications Trial, this prevalence was clearly lower. Current treatment aimed to achieve strict glycemic control has reduced the risk for developing retinopathy.

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Abbreviations: AER, albumin excretion rate; DCCT, Diabetes Control and Complications Trial; DISS, Diabetes Incidence Study in Sweden; DR, diabetic retinopathy; GADA, antibody to GAD65; IA-2A, antibody to IA-2; ICA, islet cell antibody; NPDR, nonproliferative DR; PDR, proliferative DR; WHO, World Health Organization.

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

Hyperglycemia plays a prominent part in the development of retinopathy, both in type 1 and type 2 diabetes (1,2,3). Consequently, facilitated by the use of multiple insulin injections and home blood glucose monitoring, current diabetes treatment aims to achieve strict glycemic control. One might therefore believe that early diabetic complications would have been minimized during the last decade. To elucidate this, retinal status was assessed in a nationwide population-based cohort of subjects with diabetes diagnosed in 1987–1988 at the age of 15–34 years. In this cohort study, we took advantage of the fact that islet cell antibodies (ICAs) had been measured at diagnosis (4), providing a more correct classification of the type of diabetes than if only a clinical classification had been used (5). The aims of this study were to estimate both the 10-year cumulative incidence of diabetic retinopathy and the prevalence after 10 years and to identify risk factors associated with retinopathy in patients with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Patients

Since 1983 the Diabetes Incidence Study in Sweden (DISS) has aimed to register all newly diagnosed diabetic patients nationwide in the age-group 15–34 years (6). The present investigation includes 806 subjects reported to the DISS in 1987 and 1988 (4). In 1994, all patients were contacted and asked whether they were interested in participating in a follow-up study on diabetic complications; 582 agreed to do so.

A questionnaire was sent to the patients' physicians. The requested data included information about height, weight, smoking habits, type of diabetes, current treatment, all HbA_{1c} values since diagno-

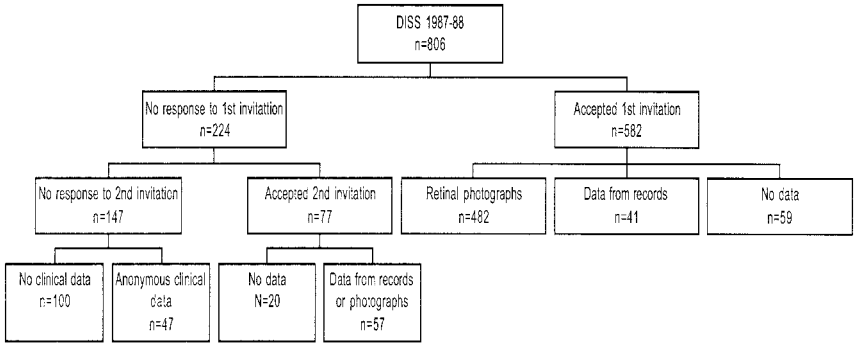

Figure 1—*Flow chart of the data generation process.*

sis, antihypertensive treatment, blood pressures, and clinical diagnosis of neuropathy and nephropathy. The patients were also asked to provide a central laboratory with a blood sample for measurement of C-peptide.

Retinopathy

Retinal status was evaluated by a central assessment of all retinal photographs taken at the patients' eye departments across the country since the diagnosis of diabetes. Retinal photographs of 482 patients were received. If no photographs had been taken, ophthalmoscopy or slit-lamp biomicroscopy data from the patient records were used ($n = 41$). Altogether, retinal data of 523 patients were available.

Patients who did not participate in the complete (i.e., questionnaire included) follow-up study ($n = 224$) were later asked to permit us to examine their retinopathy data; 77 patients consented. In 57 of the 77 patients, reliable retinal data were available from photographs or patient records. Finally, six eye departments were contacted and asked for the retinal data of the patients who did not accept the follow-up offer. In these departments, data regarding 47 patients were found and anonymously reported. Altogether, retinal data were found in 104 patients among those who did not participate in the complete follow-up study (Fig. 1).

Photographs were viewed against a light board using Donaldson's stereo viewer (5× magnification) (GJ Davco, Holbrook, MA). Two independent graders examined the photographs. If there was a disagreement, a third experienced grader determined the retinopathy level. The 11 levels of the alternative classification of the Wisconsin study were used to classify the degree of retinopathy (7,8). Level 10 represents no retinopathy, levels 21–51 nonproliferative diabetic retinopathy (NPDR) of increasing severity, and level 60+ all forms of proliferative retinopathy (PDR), with and without laser treatment. The eye with the more severe level of retinopathy decided the patient's retinopathy level. This scheme provides an 11-step scale: 10, 21/10, 21/21, 31/<31, 31/31, 41/<41, 41/41, 51/<51, 51/51, 60+/<60+, and 60+/60+ (8). The severity of retinopathy was classified into five groups: no diabetic retinopathy (level 10), very mild retinopathy (levels 21/10–21/21), mild retinopathy (31/<31–31/31), moderate-severe NPDR (levels 41/<41 to 51/51), and PDR (levels 60+/<60+ to 60+/60+). Standard photographs (2A, 3A, 8A, and 10A) were used when the retinopathy level was determined (9). Data from records were classified according to the retinopathy scale.

Type of diabetes

The classification of diabetes was made by the reporting physician according to the World Health Organization (WHO) criteria (10), without access to results of C-peptide or islet antibody determinations. The patients were classified at diagnosis (at the registration to DISS) and in the follow-up study as suffering from type 1, type 2, unclassifiable, or secondary diabetes. As a clinical classification is difficult (5,11), we also classified the patients according to the presence or absence of islet antibodies. ICA data at diagnosis have previously been reported (4). Recently, antibodies against GAD65 (GADA) and protein IA-2 (IA-2A) were determined in the samples collected at diagnosis. ICAs were determined by a prolonged immunofluorescence assay (4). GADA and IA-2A were determined by radioligand binding assays (12,13), and values of >97.5% of those in 165 healthy control subjects aged 7–35 years were considered abnormal. Patients with any of these three antibodies were considered antibody positive.

The classification of diabetic nephropathy was based on the criteria of the Swedish National Guidelines for diabetes care, i.e., at least two of three abnormal results of albumin excretion rate (AER) or notes of diabetic nephropathy in medical records. Microalbuminuria was defined as an AER of 20–200 μg/min in an overnight urinary sample. Neuropathy was registered according to the judgment of the reporting physician. Smoking was defined as current or previous daily smoking.

Local laboratories using ion-exchange chromatography measured HbA_{1c} (14). The mean (±SD) number of HbA_{1c} measurements during the 10 years was 16 ± 8.1. Random plasma C-peptide was measured at follow-up by radioimmunoassay (15). The Ethics Committee at the University of Lund approved the study.

Statistical methods

Mean HbA_{1c} was calculated using the area under the graph of HbA_{1c} over time to compensate for irregular intervals between the measurements. When analyzing differences between variables in two independent groups, the *t* test (age, HbA_{1c}, BMI, and blood pressure), the Mann-Whitney *U* test (ordinal data), and the χ^2 test (frequencies) were used. The Kaplan-Meier analysis was used to calculate the probability of retinopathy-free survival, and differences between groups were tested by the log-rank test. Correlation was assessed using the Spearman rank correlation test. To test the difference regarding any retinopathy in quartiles of HbA_{1c}, the ANOVA test was used. A Cox regression analysis was used to assess the influence of different variables on the occurrence of retinopathy. Significance was considered to be $P < 0.05$. Results were given with their 95% CIs. Data were presented as means ± SD. The statistical analyses were carried out using SPSS for Windows.

Table 1—*Clinical data at follow-up among patients with no retinopathy versus those with any retinopathy in the DISS 1987–1988 cohort*

	No DR (n = 380)	Any retinopathy (n = 247)	P
Age (years)	35.5 ± 5.8	35.1 ± 5.9	0.43
Sex (male)	224 (59%)	167 (68%)	0.03
Type of diabetes at follow up			
Type 1	231 (87)	135 (87)	0.64
Type 2	26 (10)	18 (11.5)	
Secondary	1 (0.4)	1 (0.6)	
Unclassified	8 (3)	2 (1.3)	
Insulin treatment	245 (93)	145 (95)	0.44
Mean HbA_{1c} (%)	6.8 ± 1.2	8.1 ± 1.5	<0.001
Mean BMI (kg/m^2)	24.5 ± 3.5	25.3 ± 3.6	0.05
C-peptide >0.1 nmol/l	50 (22)	24 (18)	0.41
Islet antibody positive	288 (83)	159 (85)	0.55
Smokers	97 (37)	69 (45)	0.10
Nephropathy	15 (6)	13 (8)	0.28
Peripheral neuropathy	6 (2.3)	9 (6)	0.05
Autonomic neuropathy	6 (2.3)	11 (7.1)	0.02
Blood pressure			
Systolic (mmHg)	122 ± 13	126 ± 14	0.002
Diastolic (mmHg)	75 ± 8	78 ± 9	<0.001
Systolic >130 mmHg	47 (18)	36 (24)	0.18
Diastolic >80 mmHg	37 (14)	39 (26)	0.004

Data are means ± SD or n (%). N depends on the questions answered and therefore varies.

RESULTS — Among patients with complete follow-up data, 79% had type 1, 12% type 2, and 9% unclassifiable diabetes at diagnosis. Nonparticipants in the complete follow-up had an increased prevalence of type 2 diabetes (26 and 12%, respectively; $P \leq 0.001$). Table 1 shows that among patients participating in the complete follow-up, most (94%) were insulin-treated, the prevalence of smoking was high (40%), and 5.9% of the patients had signs of nephropathy. Only 23 patients had antihypertensive treatment (mostly ACE inhibitors).

Development of retinopathy

Retinal data were obtained on 627 of the 806 patients (78%). The mean follow-up time was 9.6 ± 1.7 years for retinopathy. The median number of eye examinations by photography (82% of all examined patients) was 3 (range 1–11), with no difference between the types of diabetes. Most commonly, two to four photographic fields were taken using a wide-angle camera.

Five years after diagnosis of diabetes, there was an increase in the occurrence of retinopathy (Fig. 2*A*), with no significant difference between patients with type 1 versus type 2 diabetes. After 10 years, 247 of 627 (39%) patients were affected by retinopathy that was very mild in 136 (22%) and mild in 70 (11%), whereas 30 patients (5%) had moderate NPDR. PDR was found in 11 patients (1.8%) and sometimes occurred early (median 9 years, range 1–11); in one patient with type 2 diabetes and two with unclassifiable diabetes, it occurred within 5 years after the diagnosis of diabetes. BMI tended to be higher in patients with retinopathy who more often had neuropathy and elevated systolic and diastolic blood pressure than those without retinopathy (Table 1).

Patients with retinopathy had worse glycemic control during the study years than patients without retinopathy (HbA_{1c} 8.1 ± 1.5% vs. 6.8 ± 1.2%; $P < 0.001$). The prevalence of retinopathy increased significantly with increasing HbA_{1c} values (quartiles) ($P < 0.001$), and high levels of HbA_{1c} were associated with advanced retinopathy (Fig. 2*B*; $P < 0.001$). There was no difference in HbA_{1c} levels between men and women or between patients with or without islet antibodies. A Cox regression analysis showed that time to retinopathy was significantly shortened by increasing HbA_{1c} (RR 1.7, 95% CI 1.43–1.93; $P < 0.001$) and BMI (1.11, 1.04–1.18; $P = 0.001$).

The prevalence of retinopathy tended to be higher in cases accepting the second invitation or assessed anonymously (48 of 104 [46%]) than in those participating in the complete follow-up (199 of 523 [38%]; $P = 0.07$). The degree of retinopathy (11 levels) was most severe in those who did not participate in the complete follow-up ($P = 0.007$).

Type of diabetes and severity of retinopathy

The prevalence of severe retinopathy (moderate or severe NPDR or PDR) was significantly higher in subjects with type 2 diabetes than in those with type 1 diabetes, whether assessed at diagnosis (14 of 93[15%] vs. 24 of 471[5%]; $P < 0.001$), at follow up (16 vs. 4%); $P < 0.005$), or by the absence (type 2) versus the presence (type 1) of islet antibodies (10 of 77 [13%] vs. 21 of 397 [5.3%]; $P < 0.012$). Patients with severe retinopathy (NPDR or PDR) had significantly higher BMI ($P = 0.02$) and more often peripheral (25 vs. 2.5%) and autonomic (35 vs. 2.5%) neuropathy than those without ($P < 0.001$). The systolic and diastolic blood pressure was also higher in patients with moderate-to-severe retinopathy/PDR than in those without ($P < 0.01$).

CONCLUSIONS — The DISS is a nationwide population-based prospective study of newly diagnosed diabetes in young adults (aged 15–34 years) operating since 1983 (6) with a satisfactory ascertainment rate (16). In this study, we investigated a 2-year cohort of incident cases, and data on retinal status were available in 78% of the cohort 10 years after diagnosis. Although these young people had lived most of their lives as diabetic patients during the implementation of the conclusions of the Diabetes Control and Complications Trial (DCCT) (1) and Stockholm (2) studies, they had a high prevalence of retinopathy (39%). Nevertheless, compared with studies conducted before the DCCT, when retinopathy was reported in 63% of young diabetic patients after 8–9 years of diabetes (17), our lower prevalence indicates that current treatment aimed to achieve strict glycemic control has been successful in preventing the development of retinopathy. Besides the importance of poor

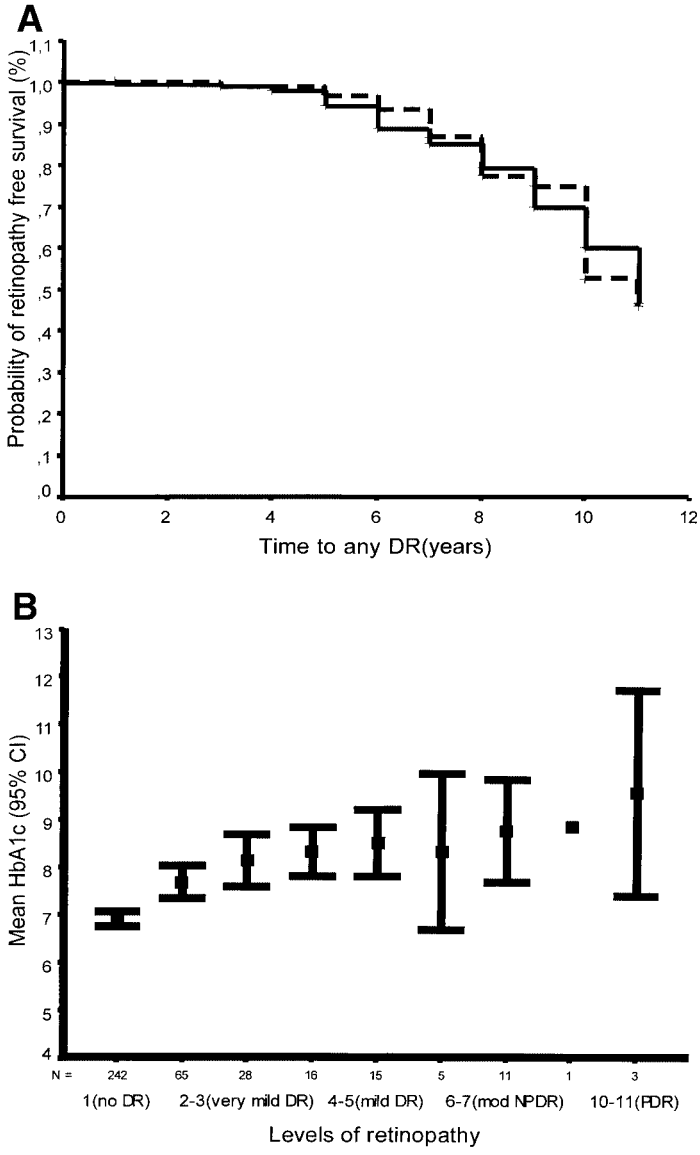

Figure 2—*A: Probability of retinopathy-free survival. Unbroken line = type 1 diabetes, broken line = type 2 diabetes, as reported at diagnosis of diabetes. Five years after diagnosis of diabetes, there was an increase in the occurrence of retinopathy with no significant difference between patients with type 1 versus type 2 diabetes.* B*: The severity of retinopathy (Wisconsin scale) in relation to mean HbA_{1c} (95% CI) during the years. Level 1, no DR; levels 2 and 3, very mild NPDR; levels 4 and 5, mild NPDR; levels 6 and 7, moderate-to-severe NPDR; levels 10 and 11, PDR. High levels of HbA_{1c} during the years were associated with advanced retinopathy* ($P < 0.001$).

glycemic control for the development of retinopathy, our study discovered other contributing factors. First, nonparticipants in the complete follow-up study had more severe retinopathy than participants. Second, using both a clinical classification and one based more objectively on islet antibodies, type 2 diabetic patients had more severe retinopathy than patients with type 1 diabetes. Third, the occurrence of retinopathy was related to high BMI, male sex, and neuropathy.

Most patients were assessed by retinal photography using standard photographs and evaluated by experienced graders. Nonparticipating individuals in the complete follow-up had a slightly higher rate of retinopathy and more often data from records than those who participated. Since photography reveals more retinal lesions than ophthalmoscopy or slit-lamp biomicroscopy (18), the prevalence of retinopathy would probably have been higher if all patients had been investigated and if retinal photographs had been used in all examinations.

A 39% prevalence of retinopathy 10 years after the diagnosis of diabetes in young adult people may be considered high. Intensive diabetes management with multiple insulin injections and home glucose monitoring was the normal practice in Sweden during the study period. As shown in the DCCT, however, intensively treated patients may develop retinopathy, though more slowly (1). Most of our patients had only developed microaneurysms during the first 10 years after diagnosis that may disappear in patients with good glycemic control (19). Nevertheless, even a few microaneurysms predict a future progression of retinopathy (20).

Interestingly, our frequency rate of retinopathy corresponds rather well to data from a clinic-based study, the EURODIAB IDDM Complications Study (21), in which ~50% of patients showed retinopathy 10 years after diagnosis. A recent Danish study found retinopathy in 60% of the patients 13 years after diagnosis (22). In the earlier Wisconsin Study from 1985 (23) and in patients who volunteered to participate in the DCCT (24), the prevalence of retinopathy was clearly higher than in this and other recent studies when related to the duration of diabetes (21,22). This indicates that current treatment, aimed to achieve normglycemia, indeed, has decreased the rate of patients developing retinopathy. This observation is further supported by the classic study of Palmberg et al. (17), who, in 1981, reported that 63% of young diabetic patients have retinopathy after 8–9 years of diabetes, a prevalence in sharp contrast to our prevalence of 39% after a similar duration of diabetes.

Proliferative retinopathy occurred in only a few patients, but in three cases, was diagnosed early in the course of the diabetes. This underlines the need for eye examinations regularly from the diagnosis of diabetes, particularly in type 2 diabetes, as recommended in American (25) guidelines. According to Swedish guidelines, a patient with adult-onset diabetes should be evaluated for retinopathy at diagnosis and then every second year (26). Our study infers that this is adequate in patients with type 2 and unclassifiable diabetes, whereas in those with type 1 diabetes, a first follow-up after 5 years may be considered as appropriate.

In agreement with the results of our study, the cumulative incidence of retinopathy did not differ between type 1 and type 2 diabetic patients in the WHO study (27). Severe retinopathy (NPDR/PDR), however, was more frequent in type 2 than in type 1 diabetic patients in our study. Patients with type 2 diabetes may have been diabetic before diagnosis (28), and therefore, the duration of diabetes may have exceeded 10 years and may explain why they had the most severe form of retinopathy.

The natural history of the microvascular complications is closely associated with metabolic control as expressed by the HbA_{1c} levels (1–3). A high glycemic burden over time leads to an increased frequency and severity of retinopathy, as clearly shown in our study. It is difficult to compare different levels of HbA_{1c} since the HbA_{1c} methods are not yet comparable between countries. Sweden uses the European standard, which, compared with the DCCT standard, is ~12% lower (29). The mean weighted HbA_{1c} level of 7.3% among our patients is the same level as the median HbA_{1c} level of ~10,000 young adult Swedish patients with type 1 diabetes according to the National Diabetes Registry of Sweden (30). The national goal for Sweden is an HbA_{1c} value of 6.5%, which corresponds to an HbA_{1c} of ~7% based on the DCCT standard. Our patients seem to have a similar control as diabetic patients in general, and data can thus be extrapolated to be true for the general young adult population with diabetes in Sweden.

In the Wisconsin Study (31), men had a slightly higher rate of retinopathy progression during 10 years. In agreement, men in our study seemed to have an increased risk of retinopathy, but in the Cox regression analysis, this risk disappeared, indicating that it might have been due to risk factors other than sex. This risk factor may be BMI, which in our study, turned out to be an obvious and significant risk factor for retinopathy. The association between a high BMI and an increased risk for retinopathy fits with the results of the DCCT (32), the WHO study (27), and a recent Belgian study (33). The reason why a high BMI was detected as a risk factor could be that our patients had fairly good metabolic control. Poor metabolic control may obscure less potent risk factors. In this context, it may be mentioned that leptin, positively associated with BMI, has been associated with proliferative retinopathy (34).

In conclusion, 10 years after diagnosis, 39% of patients demonstrated retinopathy in this nationwide cohort of young adults with diabetes, a prevalence clearly lower than that reported before the DCCT. Current treatment aimed to achieve as good glycemic control as possible has reduced the risk for developing retinopathy.

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