Improved Visual Function in IDDM Patients With Unchanged Cumulative Incidence of Sight-Threatening Diabetic Retinopathy

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OBJECTIVE — To evaluate trends in visual acuity and the cumulative incidence of diabetic retinopathy in a clinic-based observational follow-up study.

RESEARCH DESIGN AND METHODS — All patients visiting Hvidöre Hospital in 1984 whose diagnosis of IDDM had been made before 41 years of age and between 1965 and 1979 (n = 356) were followed until 1994 or until their deaths. All patients were Caucasians and resided in Copenhagen. Patients were divided into three prevalence cohorts based on time of diabetes onset: group A, 1965–1969 (n = 113); group B, 1970–1974 (n = 130); and group C, 1975–1979 (n = 113).

RESULTS — Fifteen years after diabetes onset, the visual acuity was significantly improved in patients with increasing calendar year of the disease onset. The median (interquartile range) visual acuity was 1.0 (0.8–1.0), 1.0 (0.9–1.0), and 1.0 (1.0–1.0) in groups A, B, and C, respectively ($P < 0.01$ overall; $P = 0.28$ for group A vs. group B; and $P < 0.01$ for group A vs. group C) with 60, 66, and 93 having a visual acuity of 1.0 in groups A, B, and C, respectively. The cumulative incidence (±SEM), expressed as a percentage and calculated according to the life-table method, of proliferative retinopathy, maculopathy, and laser-treated retinopathy 15 years after onset of diabetes were, respectively, 13 ± 3, 11 ± 3, and 12 ± 3 in group A; 16 ± 3, 12 ± 3, and 21 ± 4 in group B; 11 ± 3, 5 ± 2, and 12 ± 3 in group C, respectively (NS). The development of proliferative retinopathy was associated with the degree of retinopathy and albuminuria at baseline and the mean HbA_{1c} during follow-up.

CONCLUSIONS — The study revealed an improvement in visual acuity with increasing calendar year of diabetes onset but an unchanged cumulative incidence of diabetic retinopathy.

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IDDM is a chronic disease characterized by complications that include microvascular disease of the eye and the kidney. Diabetic nephropathy is the leading cause of end-stage renal disease, and diabetic retinopathy is the most important cause of visual impairment in the Western world in persons <60 years of age. Previous studies have found a cumulative incidence of diabetic nephropathy and proliferative retinopathy of 20–40% after 20–25 years of IDDM (1–5). A recent study from Sweden (6) reported a dramatic decline in the cumulative incidence of diabetic nephropathy in IDDM patients whose diagnosis was made between 1961 and 1980, when they were <15 years of age.

In a previously published study based on IDDM patients in the present patient population whose diabetes onset occurred between 1965 and 1979, we reported an unchanged cumulative incidence of diabetic nephropathy (2), in contrast to the study from Sweden. In the present study, we assessed trends in the cumulative incidence of another microangiopathic manifestation: diabetic retinopathy. In addition, we examined the related visual acuity.

RESEARCH DESIGN AND METHODS

We identified all IDDM patients attending Hvidöre Hospital in 1984 who fulfilled the following criteria: onset of IDDM occurring before 41 years of age and between 1965 and 1979, diabetes duration of >4 years, current age of >17 years, Caucasians residing in Copenhagen, not referred with proliferative retinopathy or diabetic nephropathy—a subset of a previously described cohort (7). Based on this subset of 356 patients, we have previously published a paper on the cumulative incidence of diabetic nephropathy (2). We followed patients until 1994, until they left Copenhagen, or until their deaths. Patients were divided into three cohorts based on year of diabetes onset: group A, from 1965 to 1969 (n = 113); group B, from 1970 to 1974 (n = 130); and group C, from 1975 to 1979 (n = 113). The groups were similar in regard to number, sex, social class and average HbA_{1c} from 1984 to 1994 (Table 1). The age at onset of IDDM was higher in group C compared with both groups A and B (Table 1).

Patients were seen in the clinic approximately three to four times a year from time of referral. At each visit, the postprandial blood glucose concentration, urinary glucose excretion, and body weight were measured, and the insulin dosage was adjusted. All patients received one to two daily injections of intermediate-acting insulin during the 1970s, which was increased to two to four injections of short- and intermediate-acting insulin during the 1980s. From 1985 on, most patients were treated with at least three daily injections of short-acting insulin and one injection of intermediate-acting insulin, using a pen injector. From 1973 on, patients were individually educated about diabetes in gen-

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Abbreviations: GP, general practitioner.

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

Table 1—*Clinical characteristics of 356 IDDM patients*

Group	Period of onset	Patients (*n*)	Male (%)	Age at onset (years)	HbA_{1c} in 1984–1994	Smokers in 1984 (*n*)	Social class in 1984 (%)
A	1965–1969	113	55	19.8 ± 1.0	9.0 ± 0.2	71	6/8/28/33/25
B	1970–1974	130	55	20.9 ± 0.9	8.8 ± 0.1	58	6/12/28/33/21
C	1975–1979	113	58	23.1 ± 0.8*	8.9 ± 0.1	65	4/14/25/32/25

Data are means ± SEM, unless otherwise indicated. Social class is expressed as I/II/III/IV/V according to Hansen (10). *$P < 0.05$.

eral, injection technique, and hypo- and hyperglycemia by a diabetes nurse. Education of self-monitoring of urinary glucose concentration began at the clinic in the late 1950s, and blood glucose determinations were used from 1980 on. From 1984 on, HbA_{1c} concentration was measured at least once a year by an isoelectric focusing method (normal range, 4.1–6.1%). For each patient, the yearly mean HbA_{1c} was determined and used to calculate the patient's mean HbA_{1c} in the follow-up period (from 1984 to 1994 or until the patient's death). Dietary advice was provided by a dietician; a diet containing 45–55% carbohydrates, 30–35% fat, and 15–20% protein was recommended.

Blood pressure was measured at least once a year with a standard mercury sphygmomanometer with the patient in a sitting position after 10 min of rest. Hypertension was diagnosed, and antihypertensive medication was prescribed if the mean of the last three measurements was >160/95 mmHg. Each patient had 24-h urinary albumin excretion measured at least once a year. Persistent microalbuminuria and macroalbuminuria were defined as urinary albumin excretion rates between 30 and 300 mg/24 h and >300 mg/24 h, respectively, in at least two of three consecutive samples, as recommended in a consensus report (8).

Ophthalmoscopy through dilated pupils was carried out in all patients by the same observer (E.L.) throughout the whole investigation period, from 1965 to 1988, when E.L. retired. Subsequently, 60° color fundus photographs (CF-60UV; Canon, Tokyo) of both eyes were taken after maximal dilation of the pupils in all patients, in fields 1 and 2, as defined by the Diabetic Retinopathy Study (9). Whenever maculopathy was suspected, two stereo photographs were taken with the macula in the center. The criteria for the different stages of diabetic retinopathy was kept unchanged during the whole study period. Background retinopathy was categorized as mild or more advanced. Mild background retinopathy included only red spots smaller than or equal to the diameter of the retinal arterioles. More advanced background retinopathy comprised more pronounced changes, including hemorrhages larger than the diameter of the retinal arterioles and/or soft and/or hard exudates. Proliferative retinopathy was characterized by neovascularization with or without connective tissue formation. Maculopathy was diagnosed when the patient fulfilled at least two of the following criteria: loss of visual acuity, hard exudates, and/or edema of the macula.

To evaluate the potential detection bias related to the change in method from ophthalmoscopy to fundus photography in 1988, we compared the incidence of patients who progressed in diabetic retinopathy over the following three 2-year intervals: 1984–1986 (period 1, $n = 272$), 1986–1988 (period 2, $n = 198$), and 1988–1990 (period 3, $n = 143$).

In period 1, patients were examined in both 1984 and 1986 by ophthalmoscopy. In period 2, patients were examined by ophthalmoscopy in 1986 and by fundus photography in 1988. Finally, fundus photography was used at both visits in period 3. A 2-year interval was chosen because patients with no or only mild background changes in the retina are seen every 2nd year in the eye clinic.

In this study, we used corrected visual acuity in the better eye. Until 1988, visual acuity was measured using a Snellen's chart with the patient's own refraction. If a visual acuity <1.0 was obtained, a pinhole was added, and the best obtained visual acuity with the pinhole was used. After 1988, an autorefractometer incorporating a Snellen's chart (Autorefractometer NR-7000; Nikon, Nippon Kogaku, Japan) was used to determine visual acuity after dilation of the pupil. To determine the level of agreement between visual acuity measured by Snellen's chart and the autorefractometer, we examined visual acuity using both methods in 98 consecutive patients with no or varying degrees of diabetic retinopathy who visited the eye clinic at the Steno Diabetes Centre in January 1997. The comparison of the two methods was performed in the following way. First, visual acuity was measured by Snellen's chart following the same procedure as that used before 1988. (The visual acuity was measured with the patient's own refraction. If visual acuity was <1.0, a pinhole was added, and the visual acuity was taken as that obtained with the pinhole.) The procedure was performed by the same person, who had performed it before 1988 with exactly the same equipment. Thereafter, the pupil was dilated, and visual acuity was measured using the autorefractometer. All measurements of visual acuity >1 were set to 1.

Blindness was defined as a corrected visual acuity ≤0.1 in the better eye. Patients visited the eye clinic at least once a year if diabetic retinopathy was present, and every 2nd year if retinopathy was absent. Argon or xenon laser treatment was initiated from the mid-1970s if proliferative retinopathy or maculopathy was present.

Patients were classified as smokers if they were smoking more than one cigarette in 1984.

Socioeconomic classes I–V were determined in 1984 according to the Danish National Institute of Social Research (10) based on case record information. The classification is based on personal information (and that of spouses, if applicable) regarding education, profession, and accommodation, with class I as the highest, and class V the lowest, socioeconomic class.

To evaluate potential risk factors associated with the development of proliferative retinopathy, we looked at a subgroup of patients consisting of all those without proliferative retinopathy in 1984 ($n = 313$). The exclusion of patients with proliferative retinopathy at baseline was due to the lack of valid data on albumin excretion rate, blood pressure, and HbA_{1c} before 1984. In this subgroup, we calculated for each patient a mean systolic and diastolic arterial blood pressure and a mean HbA_{1c} during follow-up (from 1984 to development of proliferative retinopathy, death, or 1994). These data from the follow-up period, together with baseline data from 1984 (degree of retinopathy [none, mild background retinopathy, or advanced background retinopathy], degree of albuminuria [normo-, micro-, or macroalbuminuria], duration of diabetes, age at onset, social class, and smoking habits), were used in a

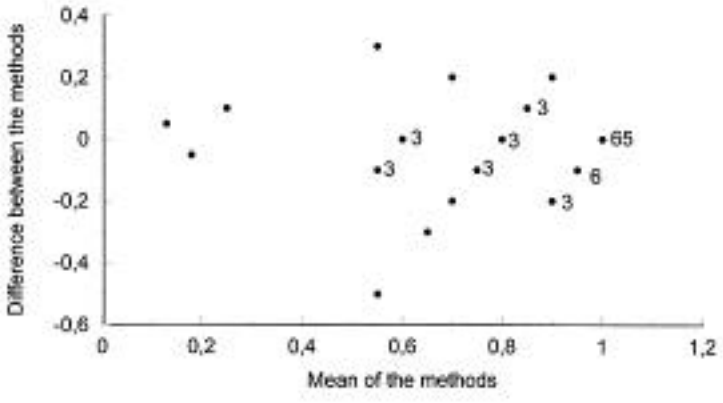

Figure 1—*Comparison of two different methods of measuring visual acuity in 98 IDDM patients who had visual acuity determined by both Snellen's chart (stenopeic hole if visual acuity < 1.0) and autorefractometer during one visit in the eye clinic. For each patient the difference in visual acuity obtained by the two methods (Snellen's chart − autorefractometer) is plotted against the mean value of the two methods [(Snellen's chart + autorefractometer)/2]. Number of patients in each point (if more than one) is indicated. A difference of zero indicates identical results by the two methods.*

stepwise multiple logistic regression analysis to determine risk factors for the development of proliferative retinopathy.

Statistical methods

Values are given as means ± SEM, and 95% CIs were calculated for observed prevalences using the binomial distribution. The cumulative incidence of the various types of diabetic retinopathy was calculated for 1-year intervals with a life-table method that accounted for differences in the interval of follow-up. The three patient groups were compared using Gehan's test. Patients in whom diabetic retinopathy did not develop were followed until 1994, until they left the Copenhagen area, or until their deaths. HbA_{1c} and age at onset in the three groups were compared using one-way analysis of variance; categorical data were compared using the χ^2 test.

The visual acuity in all three groups was compared using the Kruskal-Wallis test. The comparisons of group A versus B and of B versus C were done using the Mann-Whitney *U* test.

The association between visual acuity 15 years after onset of diabetes and potential confounders was analyzed using a multiple linear regression analysis with visual acuity as a continuous variable.

Risk factors for the development of proliferative retinopathy were analyzed in a multiple logistic regression analysis using stepwise backward selection. All calculations were performed using SPSS software (SPSS, Chicago). A P value ≤ 0.05 (two-sided) was considered significant.

RESULTS

Ophthalmoscopy versus fundus photography

To determine whether the change from ophthalmoscopy to fundus photography led to an increased sensitivity in the detection of progression in retinopathy, we compared the rate of progression of retinopathy during three different 2-year periods. In the first period, patients were examined by ophthalmoscopy at both visits with a 2-year interval (1984/1986, $n = 272$). In the second period, patients were examined by ophthalmoscopy at the first visit (1986) and by fundus photography at the second visit 2 years later (1988) ($n = 198$). In the third period, patients were examined by fundus photography at both the first visit in 1988 and the second visit in 1990 ($n = 143$).

In the comparison of patients at risk of progression to proliferative retinopathy (those with no or background retinopathy at the first visit), no significant difference was found in the percentage of patients who had progressed to proliferative retinopathy at the second visit 2 years later: 7% in period 1 (1984 [ophthalmoscopy] to 1986 [ophthalmoscopy]), 4% in period 2 (1986 [ophthalmoscopy] to 1988 [fundus photography]), and 8% in period 3 (1988 [fundus photography] to 1990 [fundus photography]). Among the patients at risk of progression to background retinopathy

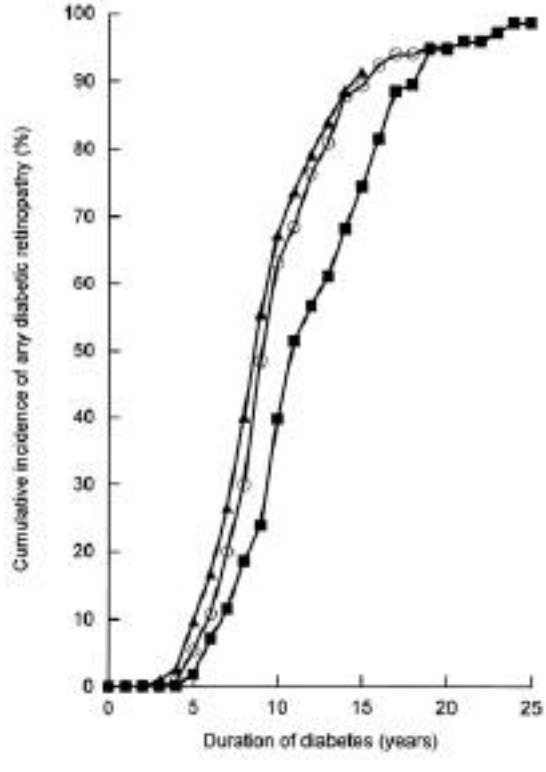

Figure 2—*Cumulative incidence of any diabetic retinopathy in 356 IDDM patients according to duration of diabetes. Patients were divided into three cohorts according to calendar year of diabetes onset: 1965–1969, n = 113 (■), 1970–1974, n = 130 (○), and 1975–1979, n = 113 (▲) (log rank NS).*

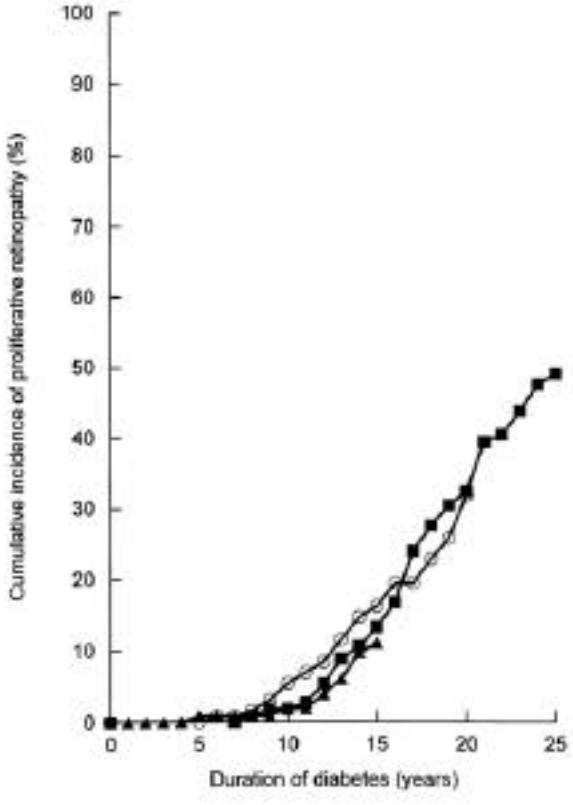

Figure 3—*Cumulative incidence of proliferative retinopathy in 356 IDDM patients according to duration of diabetes. Patients were divided into three cohorts according to calendar year of diabetes onset: 1965–1969,*n *= 113*(■)*, 1970–1974,*n *= 130*(○)*, and 1975–1979*n *= 113*(▲) *(log rank, NS).*

(those with no diabetic retinopathy at the first visit), no significant difference was found in the percentage of patients who had developed background retinopathy (30% in period 1, 23% in period 2, and 23% in period 3). Progression from no diabetic retinopathy to proliferative retinopathy was not observed in any of the three periods.

Comparison of Snellen's chart versus autorefractometer

The level of agreement between the two different methods of visual acuity determination applied during the follow-up period (Snellen's chart versus the autorefractometer) was evaluated in 98 IDDM patients with varying degrees of diabetic retinopathy. The visual acuity was determined by both methods during one visit in the eye clinic.

For corrected visual acuity in the better eye, the mean difference between measurements (95% CI) was 0.0061 (−0.015 to 0.025), and the limits of agreement were −0.29 to 0.20.

A Bland-Altman plot illustrating the level of agreement between the two methods is given in Fig. 1. For each patient, the difference in visual acuity obtained by the two methods is plotted against the mean value of the two methods. In a linear regression analysis, no correlation was found between the mean visual acuity and the difference in visual acuity obtained by the two methods. In the 98 patients examined by both methods, there was no difference in the distribution of visual acuity when compared with the distribution in visual acuity after 15 years of diabetes seen in the 356 patients with onset of diabetes between 1965 and 1979 ($P = 0.47$).

Diabetic retinopathy, maculopathy, and laser treatment

In the three cohorts of patients with diabetes onset from 1965 to 1969 (group A), 1970 to 1974 (group B), and 1975 to 79 (group C), the cumulative incidences (% ± SEM) 15 years after diabetes onset for any diabetic retinopathy were 77 ± 0.04 in group A, 89 ± 0.04 in group B, and 91 ± 0.03 in group C (NS) (Fig. 2); for proliferative retinopathy, 13 ± 1 in group A, 16 ± 3 in group B, and 11 ± 3 in group C (NS) (Fig. 3); for maculopathy, 11 ± 3 in group A, 12 ± 3 in group B, 5 ± 2 in group C (NS) (Fig. 4); and for laser-treated retinopathy, 12 ± 3 in group A, 21 ± 4 in group B, and 12 ± 3 in group C (NS) (Fig. 5).

The first cases of proliferative retinopathy occurred after 5–7 years of diabetes. Thereafter, there was a nearly constant yearly increase in the cumulative incidence of proliferative retinopathy, reaching a cumulative incidence of 50% after 25 years of diabetes. There was no tendency toward a declining incidence with increasing duration of diabetes.

In 1994, at the end of follow-up, proliferative retinopathy had developed in 54 patients (48%) of the group with onset of diabetes from 1965 to 1969 (group A), 43 (33%) with onset from 1970 to 1974 (group B), and 15 (13%) with onset from 1975 to 1979 (group C). Maculopathy was diagnosed in 26 patients (23%) of group A, 21 (16%) of group B, and 6 (5%) of group C. The numbers of patients with laser-treated retinopathy were 52 (46%) in group A, 42 (32%) in group B, and 14 (12%) in group C. Follow-up was incomplete in 58 patients (46 were lost to the study without having developed proliferative retinopathy or maculopathy) (Table 2).

Visual acuity

The visual acuity 15 years after diabetes onset was significantly improved in patients with increasing calendar year of diabetes onset (Fig. 6). The median (interquartile range) visual acuity was 1.0 (0.8–1.0) (group A), 1.0 (0.9–1.0) (group B), and 1.0 (1.0–1.0) (group C) (overall, $P < 0.01$; group A versus B, $P = 0.28$; group A versus C, $P < 0.01$) with 60, 66, and 93 having a visual acuity of 1.0 in groups A, B, and C, respectively. The number of blind patients was very small and nearly identical in the three cohorts.

To control for potential confounding variables related to the visual acuity after 15 years of diabetes we performed a multiple linear regression analysis including the following variables: calendar year of onset of diabetes, age at onset, baseline (1984) systolic and diastolic blood pressure, baseline HbA_{1c}, and baseline albuminuria (classified as normo-, micro-, and macroalbuminuria). In this model only calendar year of onset, diastolic blood pressure, albuminuria, and HbA_{1c} were significantly related to the visual acuity after 15 years of diabetes (Table 3).

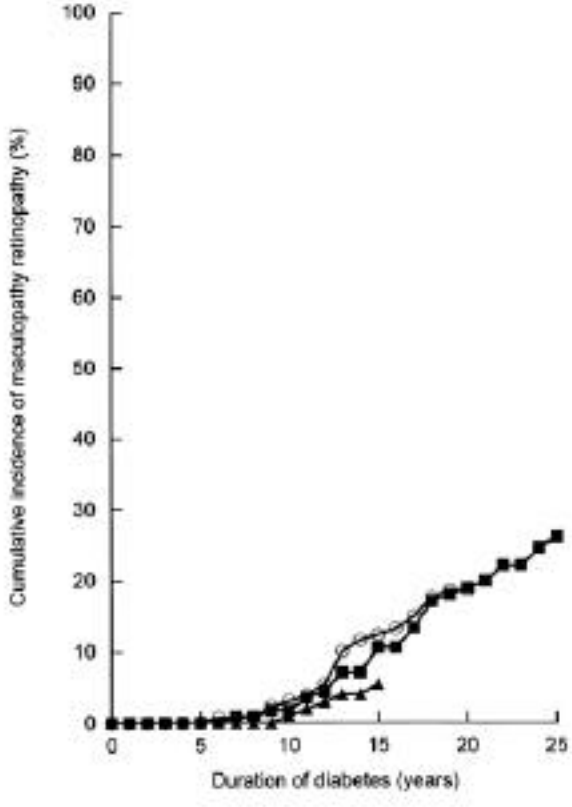

Figure 4—*Cumulative incidence of maculopathy in 356 IDDM patients according to duration of diabetes. Patients were divided into three cohorts according to calendar year of diabetes onset: 1965–1969, n = 113 (■), 1970–1974, n = 130 (○), and 1975–1979, n = 113 (▲) (log rank NS).*

Risk factors for development of diabetic retinopathy

The multiple logistic regression analysis showed a statistical significant and independent correlation between the development of proliferative retinopathy and the degree of retinopathy and albuminuria in 1984 and the mean HbA_{1c} during follow-up (from 1984 to the development of proliferative retinopathy, death, or 1994) (Table 4). The following variables were excluded from the model due to lack of statistical significance: mean systolic and diastolic blood pressure during follow-up, duration of diabetes, age at onset, smoking, and social class. If the quadrate of diabetes duration was included instead of duration, it did not reach statistical significance in the model. However, if the degree of retinopathy at baseline was omitted, the duration of diabetes became significant. If mean values of arterial blood pressure and HbA_{1c} were substituted with baseline values only, baseline degree of retinopathy and albuminuria were included in the model. Of the 313 patients included in the analysis, 69 developed proliferative retinopathy during follow-up.

CONCLUSIONS — In an observational follow-up study, we evaluated the cumulative incidences of diabetic maculopathy, background, proliferative, and laser-treated retinopathy, and visual acuity in three cohorts of IDDM patients with diabetes onset between 1965 and 1979 followed until death or 1994. We found no evidence of a so-called calendar effect, i.e., declining cumulative incidence of any of the abovementioned eye complications with increasing calendar year of diabetes onset. Patients from the most recent cohort had a significantly better visual acuity compared with patients from the oldest cohort. The three groups were similar regarding glycemic control from 1984 to 1994, degree of albuminuria, sex distribution, social class, and smoking, but the age at onset was higher in patients with onset between 1975 and 1979. In patients without proliferative retinopathy at baseline (1984), the degree of nonproliferative retinopathy and albuminuria at baseline and the mean HbA_{1c} during follow-up were found to be independent risk factors for the development of diabetic retinopathy, whereas mean systolic and diastolic blood pressure during follow-up, duration of diabetes, age at onset, smoking, and social class did not correlate significantly with the development of proliferative retinopathy. Our study confirms and extends previous investigations suggesting a lack of calendar effect, i.e., declining cumulative incidence of diabetic retinopathy with increasing calendar year of diabetes onset (3,11).

In relation to the results presented in the study, potential selection bias and detection bias should be discussed. Furthermore, our results concerning the cumulative incidence of diabetic retinopathy, the improved visual function, and finally, the risk factors for development of proliferative retinopathy are discussed and compared with findings from other studies.

Selection bias

To make a valid interpretation of our study based on a prevalence cohort of adult IDDM patients identified at Hvidöre Hospital in 1984 (7), bias due to selective referral must be accounted for. To reduce referral bias, we have only included patients from the Copenhagen area (Copenhagen municipality and county). All adult IDDM patients from this area have been referred to either Hvidöre Hospital or Steno Memorial Hospital. Treatment at both hospitals has always been free of charge, and selective bias due to socioeconomic status is therefore unlikely. Furthermore, no other treatment facilities, including private clinics or hospitals, were available in the region. In addition, the distribution of patients in socioeconomic classes in our study corresponds to the Danish background population (10). The patients are offered a life-long connection to the diabetes hospitals, since by tradition general practitioners (GPs) do not treat IDDM patients in the Copenhagen area. Therefore, selective referral of patients without complications back to the GP does not occur. Finally, a previous published comparison of IDDM patients at the Steno Diabetes Center with Danish population-based incidence and prevalence studies of IDDM found no differences with regard to age at onset and sex distribution. In addition, no differences were found in the factors influencing the size of relative mortality between the populations (12).

Detection bias

A major concern in the present study relates to potential detection bias due to the change in 1988 of visual acuity assessment and fundus grading.

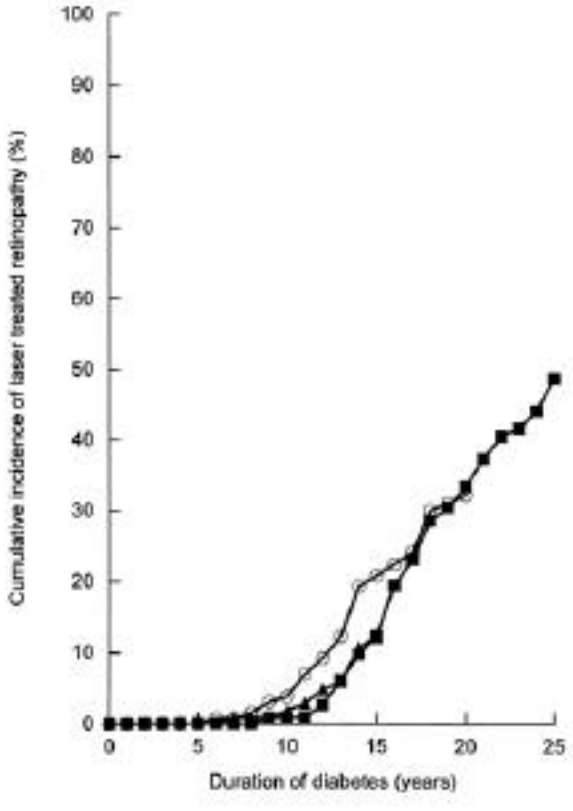

Figure 5—*Cumulative incidence of laser treated retinopathy in 356 IDDM patients according to duration of diabetes. Patients were divided into three cohorts according to calendar year of diabetes onset: 1965–1969,*n *= 113(■), 1970–1974,*n *= 130(○), and 1975–1979,*n *= 113(▲) (log rank NS).*

Visual acuity. With respect to visual acuity the two methods (Snellen's chart and autorefractometer) were compared in a representative group of diabetic patients. This comparison showed that there was no significant difference between the two methods. The comparison of the two methods was done by application of exactly the same methods as before 1988, and the same trained person was involved, to avoid person-related bias. Differences in the residual refractive error did not seem to play a role as would be expected in these groups of adult diabetic patients with 15 years of diabetes duration. Accuracy of the patients own glasses before 1988 and in 1997 might interfere with the interpretation if the glasses were in general less accurate before 1988 compared with the group of 98 patients examined in 1997. From the experience in the clinic, however, this was not the case. Thus, within the limits of accuracy of the two methods used to quantitate visual acuity, the two methods seemed comparable.

Fundus grading. With respect to the fundus evaluation, differences in classification of retinal change during follow-up is unlikely since ophthalmoscopy was carried out in all patients by the same observer (E.L.) during the investigation period from 1965 to 1988. From 1988 to 1994, color fundus photographs were evaluated by a consultant ophthalmologist in the eye care unit at the hospital using the same criteria for the classification of diabetic retinopathy as previously. Potential interobserver variation after 1988 might have affected the classification of patients within the groups. However, from 10 years of clinical experience this variation seems insignificant because of the relatively rough classification. It is possible that the introduction of the more sensitive photographic technique might have led to an earlier detection of small proliferations which were not seen by the ophthalmoscope. This would tend to increase the incidence and thus masque a real decline in the incidence of proliferative retinopathy. The comparison of the two methods (ophthalmoscopy versus fundus photography) indicated, however, that patients did not move from one classification group to another because of the method used for classification. This appeared from the fact that the rate of progression of diabetic retinopathy for the period during which patients were examined by ophthalmoscopy in 1986 and by fundus grading 2 years later was the same as the rate of progression for the period during which patients were examined by respectively ophthalmoscopy (1984/1986) and fundus grading (1988/1990) at both visits.

A true decrease in the rate of progression of diabetic retinopathy during the second method period (1986/1988) could be masked by the improved sensitivity of the fundus photographic method. However, it seems unlikely that this should occur only for the short period 1986/1988. Thus, the relatively rough classification of retinopathy applied in the present study is not affected by the change from ophthalmoscopy to fundus photography. This is in line with previous studies comparing the agreement of ophthalmoscopy versus fundus photography in the grading of diabetic retinopathy, showing that a 15-year evaluation is identical with the two methods (4,13).

Cumulative incidences of diabetic retinopathy and laser treatment

The cumulative incidences of any diabetic retinopathy of 85% and proliferative retinopathy of 13% 15 years after onset of IDDM in our study are comparable to data from previous prospective studies (5,11) and cross-sectional studies (4,14–16). In agreement with several other studies (3,4,17,18), our study showed that proliferative retinopathy is seldom found before the 10th year of IDDM. In a cross-sectional population-based survey, Klein et al. (18)

Table 2—*Status in 1994 of 356 IDDM patients*

Group	Period of onset	Patients (*n*)	Incomplete follow-up	Retinopathy	Laser-treated retinopathy	Blindness
A	1965–1969	113	19	3/26/23/48	46	7
B	1970–1974	130	13	4/47/16/33	32	1
C	1975–1979	113	18	10/72/5/13	12	1

Data are %, unless otherwise indicated. Retinopathy is presented as none/background/maculopathy/proliferative.

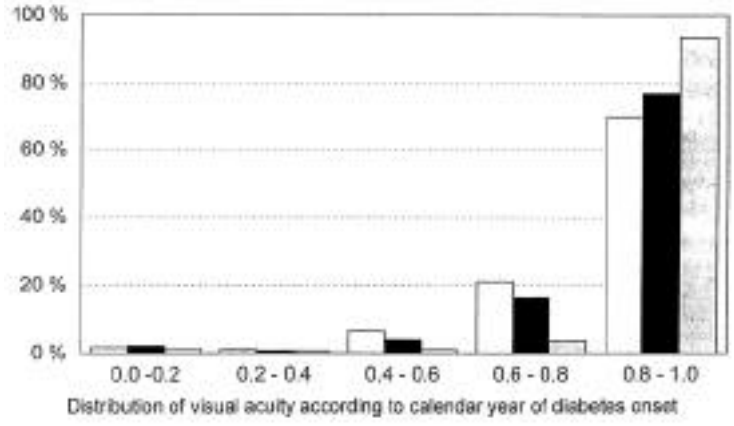

Figure 6—*Distribution of visual acuity 15 years after diabetes onset in 356 IDDM patients according to calendar year of diabetes onset (group A: 1965–1969, n = 113 [□]; group B: 1970–1974, n = 130 [■]; group C: 1975–1979, n = 113 [■]). The median (interquartile range) visual acuity was 1.0 (0.8–1.0) (group A); 1.0 (0.9–1.0) (group B); and 1.0 (1.0–1.0) (group C) (overall P < 0.01 (Kruskal-Wallis test); group A vs. B, P = 0.28; group A vs. C, P < 0.01 (Mann-Whitney U test).*

found that in patients with 15 years of IDDM, macular edema was present in 18% compared with 10% with macular edema and visual impairment in our study.

Visual acuity

The improved visual acuity 15 years after diabetes onset seen in patients with increasing calendar year of diabetes onset was found despite the three cohorts having similar cumulative incidences of proliferative retinopathy, maculopathy, and laser treatment. Furthermore, the time interval from onset of diabetes to onset of proliferative retinopathy and the initiation of laser treatment was similar in the three groups.

After adjustment for potential confounders in a multiple regression analysis, calendar year of onset remained significantly associated with visual acuity after 15 years. In addition, diastolic blood pressure, albuminuria in 1984, and HbA_{1c} in 1984 were significantly related to the visual acuity after 15 years' duration of diabetes. This analysis is weakened, however, by the fact that all patients with onset of diabetes before 1969 had their visual acuity determined before baseline in 1984. Consequently baseline values on arterial blood pressure, albuminuria, and HbA_{1c} included in the model were measured after visual acuity in these patients. Unfortunately, data on these variables were not available before 1984.

It is possible that changes in laser treatment procedures during follow-up might play a role for the improved visual acuity. Unfortunately, the present registration of laser treatment does not differentiate between the amount of treatment and whether treatment was given in the periphery or the macular region. After 1988, laser treatment of the macular region was performed according to the ETDRS (19) recommendations, and thus changes in laser treatment procedures may be one explanation for the increased visual acuity in the cohort of patients with latest onset of diabetes. Earlier cataract operations, vitrectomies, the use of ACE inhibitors, and generally more aggressive antihypertensive treatment are other explanations for the improved vision. Recently Bäcklund et al. (20) reported a reduction of new blindness in diabetes by more than one-third in Stockholm County, attaining one of the main targets of the St. Vincent Declaration, made during the Diabetes Care and Research in Europe project in 1989.

Risk factors for the development of proliferative retinopathy

We found a significant relationship between the mean HbA_{1c} during follow-up and the development of proliferative retinopathy. A 1% increase in mean HbA_{1c} during follow-up was associated with a 48% increased risk for the development of proliferative retinopathy. Poor glycemic control has been demonstrated in several studies to be related to an increased risk of developing diabetic complications (22,23). The Diabetes Control and Complications Trial (DCCT) (24) and several smaller randomized intervention studies (25) have demonstrated the beneficial effect of strict glycemic control as a means of preventing or delaying development of any degree of diabetic retinopathy.

The present finding of an association between albuminuria and the development of proliferative retinopathy has been demonstrated previously in other studies (26–28). The association between albuminuria and the development of proliferative retinopathy is in agreement with the Steno hypothesis (29) suggesting that increased albuminuria reflects a widespread vascular damage due to genetically determined alterations in the composition of the extracellular matrix leading to the micro- and macroangiopathic complications associated with diabetes.

The progression of diabetic retinopathy is a continuous process, making the degree of vascular changes in the retina at baseline (1984) an obvious risk factor for the development of proliferative retinopathy. Interestingly, however, even mild vascular abnormalities at baseline represent a strong predictor for future progression to proliferative changes, stressing the importance of regular eye examination of these patients.

Previous studies of the association between blood pressure and the develop-

Table 3—*Factors associated with visual acuity 15 years after diabetes onset*

	Correlation coefficient (95% CI)	*P* value
Calendar year of diabetes onset	−0.0075 (−0.0122 to −0.00266)	0.002
Diastolic blood pressure at baseline (increase of 1 mmHg)	0.0025 (0.0004 to 0.0045)	0.019
HbA_{1c} at baseline (increase of 1%)	0.0225 (0.0128 to 0.0322)	0.0001
Albuminuria at baseline (normo-, micro-, and macroalbuminuria)	0.0387 (0.0107 to 0.0667)	0.006

Systolic blood pressure in 1984 and age at onset of diabetes did not reach statistical significance ($R^2 = 0.17$; adjusted $R^2 = 0.16$).

Table 4—*Risk factors for the development of proliferative retinopathy*

	Relative risk (95% CI)	*P* value
Retinopathy		
Mild background vs. none	9.36 (3.02–29.60)	0.0001
Advanced background vs. none	15.7 (5.10–48.70)	0.00001
Degree of albuminuria		
Micro- vs. normoalbuminuria	1.68 (0.80–3.51)	NS
Macro- vs. normoalbuminuria	6.06 (2.05–17.90)	0.001
Increase of 1% in mean HbA_{1c} during follow-up	1.48 (1.11–1.97)	0.008

Only patients without proliferative retinopathy at baseline (n = 313) were included in the analysis. Of these, 69 developed proliferative retinopathy during follow-up.

ment of diabetic retinopathy have not produced uniform findings (14,15,28,30,31) probably due to differences in study design (cross-sectional versus prospective) and patient population. In addition, the studies vary in the number of confounding variables taken into account. In our study, arterial blood pressure was significantly related to the development of proliferative retinopathy in a univariate analysis whereas the association became insignificant when other explaining factors were included in a multivariate analysis. In the multivariate analysis, the relative risk for proliferative retinopathy associated with a 10-mmHg increase in mean arterial blood pressure was 1.47 (95% CI, 0.78–1.69; NS).

One explanation for the lack of association might be a rather well-controlled blood pressure in our population with 25% using antihypertensive medication obscuring any potential association. However, in agreement with other studies (32,33), there was an association in the subgroup suffering from diabetic nephropathy suggesting that these patients are particularly susceptible to elevated arterial blood pressure. Nørgaard et al. (33) further suggested that the apparent association of retinopathy with hypertension seen in cross-sectional studies and studies with long intervals between follow-up, appears only because of the close time relationships between increase in urinary albumin excretion rate and blood pressure, the former preceding the latter.

Some studies have found an association between smoking and the development of diabetic retinopathy (34,35) whereas other have not confirmed this finding (36–38). In our study, there was a very high percentage of smokers (65%), which is higher than the Danish background population (46% in 1984) (10). We found no significant impact of smoking on the development of proliferative retinopathy.

In conclusion, our study revealed an improved visual acuity with increasing calendar year of diabetes onset but an unchanged cumulative incidence of sight-threatening diabetic retinopathy in patients with IDDM onset from 1965 to 1979. Increased albuminuria and background retinopathy at baseline together with poor glycemic control during follow-up were associated with increased risk of developing proliferative diabetic nephropathy.

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