The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: The Twenty-five-Year Incidence of Macular Edema in Persons with Type 1 Diabetes

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Objective: To examine the 25-year cumulative incidence of macular edema (ME) and its relation to various risk factors.

Design: Population-based study.

Participants: A total of 955 insulin-taking persons living in an 11-county area in southern Wisconsin with type 1 diabetes diagnosed before age 30 years who participated in baseline examinations (1980–1982) and at least 1 of 4 follow-up (4-, 10-, 14-, and 25-year) examinations (n = 891) or died before the first follow-up examination (n = 64).

Methods: Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme. Competing risk of death was included in statistical models.

Main Outcome Measures: Incidence of ME and clinically significant ME (CSME).

Results: The 25-year cumulative incidence was 29% for ME and 17% for CSME. Annualized incidences of ME were 2.3%, 2.1%, 2.3%, and 0.9% in the first, second, third, and fourth follow-up periods of the study, respectively. In univariate analyses, the incidence of ME was associated with male sex, more severe diabetic retinopathy, higher glycosylated hemoglobin, proteinuria, higher systolic and diastolic blood pressure, and more pack-years of smoking. Multivariate analyses showed that the incidence of ME was related to higher baseline glycosylated hemoglobin (hazard ratio [HR] per 1% 1.17; 95% confidence interval [CI], 1.10–1.25; $P<0.001$) and higher systolic blood pressure (HR per 10 mmHg 1.15; 95% CI, 1.04–1.26; $P = 0.004$) and marginally to proteinuria (HR 1.43; 95% CI, 0.99–2.08; $P = 0.06$).

Conclusions: These data show that relatively high 25-year cumulative rates of incidence of ME were related to glycemia and blood pressure. The lower risk of incident ME in the last period of the study may reflect recent improvement in care.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2009;116:497–503 © 2009 by the American Academy of Ophthalmology.*

Macular edema (ME) is an important cause of visual impairment in persons with diabetes.[1–3] Although a number of studies have described the incidence of ME and its relationship to various risk factors such as glycemia and blood pressure, few have been in cohorts of persons with type 1 diabetes followed over a long period.[4–17] Recent changes in the incidence of ME would be expected with the more widespread use of intensive glycemic and blood pressure control.[1,18–21] In this report, we extend our previous observations by describing the 25-year incidence of ME and changes in the prevalence and incidence of ME in a large cohort of persons with type 1 diabetes mellitus participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).[8–10]

Materials and Methods

Study Population

The population, who have been described in previous reports,[10,22–28] consisted of a sample selected from 10,135 diabetic patients who received primary care in an 11-county area in southern Wisconsin from 1979 to 1980. This sample was composed of all persons with "younger-onset" diabetes and a duration-stratified sample of persons with "older-onset" diabetes. The analyses in this report are limited to the group with younger-onset diabetes, all of whom were taking insulin and had been diagnosed before 30 years of age (n = 1210). There were 996 persons in this group who participated in the baseline examination (1980–1982),[23] 903 persons in the 4-year follow-up,[25] 816 persons in the 10-year follow-up,[26] 667 persons in the 14-year follow-up,[26] 567 persons in the 20-year follow-up,[27] and 520 persons in the 25-year follow-up.[28] The reasons for nonparticipation and comparisons between participants and nonparticipants at baseline and the 4-, 10-, and 14-, and 20-year follow-ups have been presented.[10,23,25–27] Retinopathy data were not collected at the 20-year follow-up, so information from that examination is not included in this report. For the 25-year follow-up, the reasons for nonparticipation have been presented.[28]

Procedures

The baseline and follow-up examinations were performed in a mobile examination van in or near the city where the participants

ISSN 0161-6420/09/$–see front matter
doi:10.1016/j.ophtha.2008.10.016

resided. All examinations followed a similar protocol that was approved by the institutional human subjects committee of the University of Wisconsin and conformed to the tenets of the Declaration of Helsinki. The pertinent parts of the ocular and physical examinations included measuring weight, height, and blood pressure,[29] dilating the pupils, taking stereoscopic color fundus photographs of 7 standard fields[30,31] (not done at the 20-year follow-up), performing a semiquantitative determination of protein levels in the urine using Labstix (Ames, Elkhart, IN), and determining blood glucose and glycosylated hemoglobin A1 levels from a capillary blood sample at the baseline, 4-, 10-, and 14-year follow-ups and glycosylated hemoglobin A1c from venous blood at the 20- and 25-year follow-ups (Quick Step Fast Hemoglobin Test System, Isolab, Akron, OH).[32,33] The normal range for glycosylated hemoglobin A1 was 4.6% to 7.9%. Its intra-assay coefficient of variation was 2.4%. The WESDR glycosylated hemoglobin A1 microcolumn results compare with the Diabetes Control and Complications Trial (DCCT) glycosylated hemoglobin A1c results as follows: DCCT = 0.003 + 0.935 (WESDR).[32]

Examiners conducted a structured interview that included questions about specific medications for control of hyperglycemia and blood pressure, the number of aspirin used during the 30 days before the baseline examination, and smoking history. If there was any question about medication use, it was verified by a physician's report.

Grading Protocol

Grading protocols have been described in detail elsewhere[25,34] and are modifications of the Early Treatment Diabetic Retinopathy Study adaptation of the modified Airlie House classification of diabetic retinopathy (DR).[35,36] Interobserver and intraobserver variations and the validity of the systems have been evaluated, and the results have been presented.[25,34,36,37]

Definitions

For each eye, the maximum grade in any of the 7 standard photographic fields was determined for each of the lesions and used in defining the "retinopathy levels." This has been described in detail.[26,36] In brief, 13 levels of increasing DR severity from none to end-stage proliferative DR with loss of vision (10, 21, 31, 37, 43, 47, 53, 60, 61, 65, 71, 75, 85) were assigned to each. The DR level for a participant was derived by concatenating the levels for the 2 eyes, giving the eye with the higher level greater weight. This scheme provided a 15-step scale (10/10, 21/<21, 21/21, 31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60+/<60+, and 60+/60+) when all levels of proliferative DR are grouped as 1 level. For purposes of classification, if the DR severity could not be graded in an eye, it was considered to have a score equivalent to that of the other eye.

Macular edema was defined as retinal thickening in the macular area, and clinically significant macular edema (CSME) was defined according to the Early Treatment Diabetic Retinopathy Study classification protocol as the presence of retinal thickening at or within 500 μm of the center of the macula or hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina or zones of retinal thickening 1 disc area in size, at least part of which was within 1 disc diameter of the center. The cumulative incidence of ME was estimated from all persons who had no ME, and the cumulative incidence of CSME was estimated from all persons who had no CSME at the baseline who participated in the follow-up examination(s).

Age was defined as the age at the time of the baseline examination. Age at diagnosis of diabetes was defined as the age at the time the diagnosis was first recorded by a physician on the patient's chart or in a hospital record. The duration of diabetes was that period between the age at diagnosis and the age at the baseline examination.

Systolic and diastolic blood pressures were the average of the 2 measurements taken according to the protocol of the Hypertension Detection and Follow-Up Program protocol.[29] Hypertension was defined as a mean systolic blood pressure ≥160 mmHg, a mean diastolic blood pressure ≥95 mmHg, or a history of antihypertensive medication at the time of examination for individuals ≥25 years of age and a mean systolic blood pressure of ≥140 mmHg, a mean diastolic blood pressure of ≥90 mmHg, or a history of antihypertensive medication at the time of examination in younger persons.

A person was classified as a never smoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime, as an ex-smoker if he/she smoked more than this number of cigarettes in his/her lifetime but had stopped smoking before the examination, and as a current smoker if he/she had not stopped. Pack-years smoked was calculated as the number of cigarettes smoked per day divided by 20, multiplied by the number of years of smoking from the time of diagnosis of diabetes. Body mass index (BMI) was defined as weight in kilograms divided by the height in meters squared. Proteinuria was defined as urine protein concentration of 30 mg/dl or greater as measured by Labstix.

Statistical Methods

Cumulative 25-year incidence rates were calculated with a competing risk approach (a modification of the Kaplan–Meier approach) to account for censored observations because of missed examinations and the competing risk of death.[38] Estimated incidence between examinations were converted to an average annual rate using the formula: $1-(1-p_n)^{1/n}$, where n is the number of years between examinations and p_n is the cumulative incidence between examinations.

For multivariable analyses, we used a generalized linear model for the binary outcomes (incidence during the examination interval) with the complementary log-log link function to estimate an underlying continuous-time proportional hazard model while accounting for the varying follow-up times between examinations. For these analyses, duration of diabetes was the time variable, and the baseline hazard was assumed to be piecewise constant within 5-year bands of diabetes duration starting at 10 years and continuing to >40 years. Hazard ratio (HR) estimates were calculated by exponentiation of estimated coefficients. PROC NLMIXED of SAS version 9.1 (Cary, NC) was used for these analyses.

Variables included in the multivariable analyses were selected in stepwise fashion from the following list: age at diagnosis, sex, glycosylated hemoglobin, systolic and diastolic blood pressure, hypertension, gross proteinuria, and BMI. These models were rerun including severity of retinopathy at baseline. Continuous variables were included as linear terms. Two sets of models were considered: (1) models including only baseline characteristics and (2) models using time-varying covariates updated at each follow-up examination (i.e., for each time interval in which a subject participated, the values of the risk factors at the beginning of the interval were used).[39]

Results

Characteristics of the Cohort

Characteristics at the baseline examination of those who participated in the 25-year follow-up, those who did not participate because they could not be located or they refused, and those who had died in the 11-year interval between the 14- and 25-year examinations have been presented elsewhere.[28] With the exception

Table 1. Twenty-five-Year Cumulative Incidence of Macular Edema and Clinically Significant Macular Edema by Age and Duration of Diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy

	Incidence of ME				Incidence of CSME			
			Cumulative Incidence (%)				Cumulative Incidence (%)	
	No. at Risk	*No. Events*	*Event*	*Risk of Dying before Event*	*No. at Risk*	*No. Events*	*Event*	*Risk of Dying before Event*
All groups	818	213	28.6	25.3	841	128	16.6	29.0
Age								
0–9 y	24	4	23.2	0.0	24	4	23.2	0.0
10–14 y	77	18	28.8	10.4	77	12	19.0	12.4
15–19 y	142	34	26.1	13.7	143	23	17.7	15.2
20–24 y	141	39	29.7	11.9	143	25	18.4	13.5
25–29 y	111	40	39.9	15.7	117	23	21.1	21.3
30–34 y	122	33	29.9	21.0	125	19	16.5	25.1
35+ y	201	45	23.4	57.5	212	22	11.0	63.0
Diabetes Duration								
0–2 y	74	11	17.7	9.6	74	6	10.2	11.5
3–4 y	80	19	29.2	10.0	80	10	14.4	11.9
5–9 y	234	72	34.0	9.3	235	56	26.4	11.8
10–14 y	142	50	37.7	14.1	146	25	18.1	16.0
15–19 y	100	24	26.1	30.2	103	12	12.3	35.1
20–24 y	60	20	36.0	38.8	68	12	19.5	45.0
25–29 y	54	10	19.1	59.8	57	6	10.7	63.6
30+ y	74	7	9.6	82.8	78	1	1.3	88.3

ME = macular edema; CSME = clinically significant macular edema.

of less education, there were no significant differences in the characteristics of those who participated compared with those who survived but did not participate. The 120 persons with younger-onset diabetes who died in the interval between the 14- and 25-year follow-up examinations were older and had longer duration of diabetes, higher glycosylated hemoglobin, proteinuria, higher systolic blood pressure, greater BMI, more pack-years of smoking, more severe retinopathy, and poorer visual acuity than those who participated (data not shown). The frequency of focal and macular grid photocoagulation was not significantly different in those who died compared with those who participated (data not shown).

Factors Associated with the Cumulative Incidence of ME

The 25-year cumulative incidence of ME in the population accounting for the competing risk of death was 29% (95% confidence interval [CI], 25–32), and the 25-year cumulative incidence of CSME was 17% (95% CI, 14–19). Cumulative incidence of ME was not linearly related to age and duration of diabetes at baseline (Table 1). The competing risk of death increased with age and duration at baseline (Table 1).

The estimates of the annual incidence of ME and CSME over the 4 study intervals are presented in Figure 1. The an-

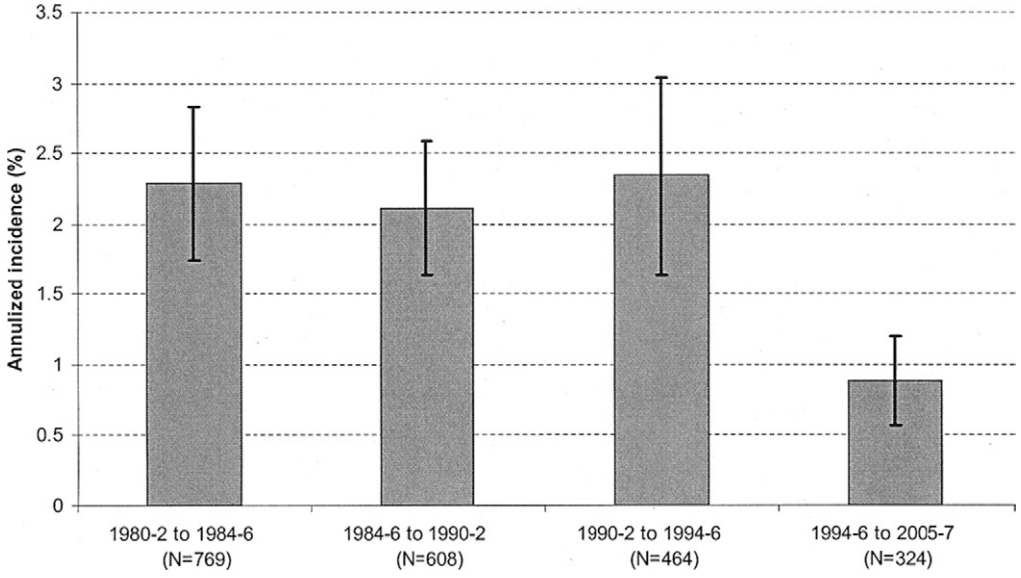

Figure 1. Estimated annual rates for incidence of ME for 4 periods of the WESDR.

Table 2. Associations with Incidence of Macular Edema

Risk Variable	Level	Univariate			Multivariate*		
		HR	*95% CI*	P	*HR*	*95% CI*	P
Sex	Male	1.32	1.02–1.72	0.04			
Age at diagnosis	10–19 y vs. <10 y	1.32	0.96–1.82	0.09			
	20–29 y vs. <10 y	1.32	0.92–1.90	0.13			
Glycosylated hemoglobin A_1	Per 1%	1.17	1.10–1.25	<0.001	1.17	1.10–1.25	<0.001
Glycosylated hemoglobin A_1 quartiles	9.5–10.5 vs. <9.5%	1.54	1.00–2.39	0.05			
	10.6–12.0 vs. <9.5%	2.17	1.46–3.22	<0.001			
	12.1–19.5 vs. <9.5%	2.50	1.67–3.72	<0.001			
Proteinuria	Present	1.68	1.19–2.37	0.003	1.43	0.99–2.08	0.056
Retinopathy severity	21 vs. 10	1.52	1.00–2.32	0.05			
	31–37 vs. 10	2.71	1.85–3.95	<0.001			
	43–53 vs. 10	3.26	2.08–5.11	<0.001			
	60+ vs. 10	3.40	2.06–5.62	<0.001			
Systolic blood pressure	Per 10 mmHg	1.15	1.06–1.25	0.001	1.15	1.04–1.26	0.004
Diastolic blood pressure	Per 10 mmHg	1.16	1.02–1.32	0.02			
Hypertension	Present	1.20	0.83–1.74	0.34			
Smoking history†	Past vs. never	0.72	0.44–1.17	0.18			
	Current vs. never	1.13	0.81–1.57	0.47			
Pack-years smoked†	<5 pack-years	0.85	0.55–1.32	0.47			
	5–14 pack-years vs. never	0.94	0.58–1.53	0.81			
	≥15 pack-years vs. never	1.67	1.03–2.69	0.04			
Education	Per 4 y	1.15	1.00–1.32	0.06			
BMI	Per 4 kg/m^2	1.09	0.97–1.23	0.16			

HR = hazard ratio; CI = confidence interval; BMI = body mass index.
*All variables except retinopathy severity not included in a single model. Missing rows indicate that variable was not significant, and thus not included in the final multivariate model.
†Univariate model also controls for age.

nualized estimates were lowest in the last period of observation.

In univariate analyses, male sex, more severe DR, higher glycosylated hemoglobin, proteinuria, higher systolic and diastolic blood pressure, and history of smoking more pack-years at baseline were significantly associated with the incidence of ME (Table 2). Hypertension, BMI, smoking status, history of aspirin use (data not shown), history of diuretics use (data not shown), and education level at baseline were not associated with incidence of ME (Table 2). Multivariate analyses showed that having a higher glycosylated hemoglobin and higher systolic blood pressure were statistically significantly related and proteinuria marginally related to the incidence of ME (Table 2). When DR severity was added to the model, only glycosylated hemoglobin (HR per percent increase 1.15; 95% CI, 1.08–1.23; $P<0.001$) and DR severity (HR per 2 step increase 1.19; 95% CI, 1.12–1.29; $P<0.001$) were associated with the incidence of ME over a 25-year period. While controlling for baseline glycosylated hemoglobin and retinopathy severity, only a change in glycosylated hemoglobin (HR per 1% 1.22; 95% CI, 1.14–1.31; $P<0.001$) between baseline and the 4-year follow-up was associated with ME over a 21-year period.

Time-varying covariate analyses generally showed associations similar to those found with analyses using only baseline covariates. Glycosylated hemoglobin (HR per 1% 1.37; 95% CI 1.29–1.45; $P<.001$), proteinuria (HR 1.56; 95% CI, 1.14–2.15; $P = 0.006$), systolic blood pressure (HR per 10 mmHg 1.15; 95% CI, 1.06–1.25; $P = 0.001$), and diastolic blood pressure (HR per 10 mmHg 1.24; 95% CI, 1.09–1.42; $P<0.001$) were associated with incident ME but not hypertension (HR 1.31; 95% CI, 0.94–1.81; $P = 0.11$), smoking status (HR past vs. never 0.77; 95% CI, 0.51–1.41; $P = 0.20$ and HR current vs. never 1.07; 95% CI, 0.77–1.69; $P = 0.69$), or BMI (HR per 1 kg/m^2 0.93; 95% CI, 0.81–1.07; $P = 0.32$).

Changes in Prevalence of ME and CSME by Year at Diagnosis

There was no statistically significant relation of prevalence of ME or CSME by year of diabetes diagnosis and duration of diabetes in the cohort (data not shown).

Discussion

The data reported provide long-term population-based information regarding the 25-year cumulative incidence of ME and its relationship to glycemia, blood pressure, proteinuria, and other factors in persons with type 1 diabetes mellitus. The 25-year incidence of ME (29%) and CSME (17%) were high, and the strongest and most consistent associations were with glycemia and to a lesser extent systolic and diastolic blood pressure and nephropathy as manifest by gross proteinuria. Lower annualized incidence of ME and CSME was found in the last period of follow-up compared with earlier periods of follow-up.

On the basis of our findings, we would estimate that over a 25-year study period, of the 515,000 to 1.3 million Americans thought at present to have type 1 diabetes, approximately 149,000 to 377,000 will develop ME and 88,000 to 221,000 will develop CSME (NIDDK Clearing House http://www.medhelp.org/NIHlib/GF-254.html#four, accessed September 16, 2008). The decline in estimated annualized incidence of ME and CSME between the 1994–1995 and 2005–2006 examinations from earlier periods suggest the possibility that

applying these figures to persons who currently have type 1 diabetes may overestimate the number of persons who will develop ME over the next 25 years. There are few other population-based studies in which incidence data collected over a long period of time using objective measures have been used to detect changes in incidence of ME. Data from a clinic-based study in Denmark showed a decline in the incidence of ME in persons who were more recently diagnosed to have diabetes.[18] This decline was associated with statistically significant trends of decreasing glycosylated hemoglobin, mean arterial blood pressure levels, and earlier treatment of hypertension. In the WESDR, a reason for the decline in incident CSME may involve better glycemic control.[40] This is suggested by lower levels of mean glycosylated hemoglobin A1 (from 10.7% in the first period to 9.4% in the fourth period) in those at risk of developing ME in more recent periods compared with earlier periods of the study (Klein R, unpublished data, June 30, 2008). This is likely the result of data from randomized clinical control trials demonstrating a beneficial effect of intensive glycemic control on reducing the incidence of ME in persons with type 1 diabetes.[12] However, changes in levels of mean systolic blood pressure (from 120.4 mmHg in the first period to 124.4 mmHg in the fourth period) in those at risk of developing ME in more recent periods compared with earlier periods of the WESDR were unlikely to explain the reduction of incidence of ME in persons with type 1 diabetes in more recent periods (Klein R, unpublished data, June 30, 2008). Alternatively, the decline in incidence of ME in the latest period of the WESDR may be a result of death leading to selection of the healthiest. This is suggested by the finding that those who had died in the interval between the 14- and 25-year follow-up examinations were older and had longer duration of diabetes, higher glycosylated hemoglobin, proteinuria, higher systolic blood pressure, greater BMI, more pack-years of smoking, more severe retinopathy, and poorer visual acuity than those who participated. This information is important in planning for counseling and rehabilitative services, projecting costs, measuring temporal trends, developing causal inferences, and providing sample size estimates for conducting clinical trials. For example, if there is a "true" decrease in the incidence of CSME in persons with type 1 diabetes, there may be a need for fewer health care resources to detect and treat these individuals with focal or macular grid photocoagulation. It is also important to emphasize caution when using these data to estimate sample sizes needed to evaluate efficacy of new treatments in reducing the incidence of ME in clinical trials. Our WESDR population, first examined approximately 30 years ago in 1980–1982, is likely to not be representative of contemporary populations of persons newly diagnosed with type 1 diabetes because more emphasis today is placed on intensive control of glycemia, blood pressure, and lipids, and more aggressive management of renal disease.

Hyperglycemia, at baseline and throughout the study period, was associated strongly with the incidence of ME. This was not surprising given our earlier findings and those from the DCCT/Epidemiology of Diabetes Interventions and Complications and other studies.[8–13,41] In our study, hyperglycemia was similarly associated with incidence of ME at all examinations, suggesting that lower levels of glycosylated hemoglobin were associated with lower incidence regardless of duration of diabetes. An increase of 1% in the glycosylated hemoglobin between baseline and follow-up was associated with a 22% increase in the 21-year cumulative incidence of ME. This is consistent with data from the DCCT that found intensive glycemic control was associated with a 46% reduction in the incidence of ME at the end of the trial and a 58% reduction 4 years later in people with type 1 diabetes compared with those in the conventional group.[12]

In our study, systolic blood pressure, but not the presence of hypertension, was associated with the incidence of ME. Blood pressure has inconsistently been found to be associated with the prevalence and incidence of ME in persons with type 1 diabetes.[8–11,13,16,41] Selective mortality may be attenuating the relationship of blood pressure and hypertension to the incidence of ME in the current study, that is, participants with high blood pressure who developed ME may have died in the 11-year interval between the 14- and 25-year examinations before being examined.

Proteinuria, independent of glycemia and blood pressure, was found to be marginally associated with the incidence of ME in the WESDR. This is consistent with data from most studies that showed associations between the prevalence of diabetic nephropathy, as manifest by microalbuminuria or gross proteinuria, and the incidence and progression of DR.[23,26,42–48] There are also anecdotal reports of patients with renal failure having more severe ME that improves after dialysis or renal transplantation. Rheologic, lipid, and platelet abnormalities associated with nephropathy may be involved in the pathogenesis of ME.

We had hypothesized that smoking, through its effect on coagulation and inflammatory pathways leading to hypoxia and exudation, would increase the risk of developing ME.[49–52] Although we found a univariate relation of higher incidence of ME in those with a history of the highest amount of smoking exposure (≥15 pack-years of smoking after diagnosis of diabetes) in the WESDR, this relationship was attenuated and no longer statistically significant in multivariate analyses. This is consistent with our earlier findings and with those from others showing no relationship of smoking to incidence and progression of DR or ME.[48,53–55] The reasons for not finding a relation are not known. Regardless, smoking should be avoided because of its relation to increased risk of death and other systemic complications.

There are many strengths of the study, including a large cohort with a broad distribution of severity of retinopathy at baseline, a low refusal rate, and the use of standardized protocols of measurement that included objective recording of ME using stereoscopic fundus photographs of 7 standard fields. However, caution should be observed when interpreting the findings from our study. Mortality may affect the relation of risk factors to incidence of end points. Because glycosylated hemoglobin, blood pressure, gross proteinuria, and retinopathy severity level are significantly associated with incidence of ME and decreased survival,[40] it is likely that the effect of death would diminish the strength of these relationships. Also, serum lipids were not measured at baseline, limiting our ability to examine the relation of this risk factor to the 25-year cumulative incidence of ME.

Our data suggest that better glycemic and blood pressure control at baseline and throughout the study may be beneficial in reducing the incidence of ME. In addition, our data show a reduction in the incidence of ME in the latest period of follow-up, suggesting a possible benefit of recent changes in management of diabetes on the incidence of ME, although it may, in part, reflect survival of the healthiest.

References

1. Klein R, Klein BE. Vision disorders in diabetes. In: National Diabetes Data Group. Diabetes in America. 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:293–338. NIH Publication No. 95–1468.
2. Tielsch JA. Prevent Blindness America. Vision Problems in the U.S: A Report on Blindness and Vision Impairment in Adults Age 40 and Older. Schaumburg, IL: Prevent Blindness America; 1995:1–20.
3. Moss SE, Klein R, Klein BE. Ten-year incidence of visual loss in a diabetic population. Ophthalmology 1994;101:1061–70.
4. Aiello LM, Rand LI, Briones JC, et al. Diabetic retinopathy in Joslin Clinic patients with adult-onset diabetes. Ophthalmology 1981;88:619–23.
5. Myers FL, Davis MD, Magli YL. The natural course of diabetic retinopathy: a clinical study of 321 eyes followed one year or more. In: Goldberg MF, Fine SL, eds. Symposium on the Treatment of Diabetic Retinopathy. Arlington, VA: U.S. Neurological and Sensory Disease Control Program; 1969: 81–5. PHS publication 1890.
6. Kohner EM. The evolution and natural history of diabetic retinopathy. Int Ophthalmol Clin 1978;18:1–16.
7. Sigelman J. Diabetic macular edema in juvenile- and adult-onset diabetes. Am J Ophthalmol 1980;90:287–96.
8. Klein R, Moss SE, Klein BE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XI. The incidence of macular edema. Ophthalmology 1989;96:1501–10.
9. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. Ophthalmology 1995;102:7–16.
10. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology 1998;105:1801–15.
11. Vitale S, Maguire MG, Murphy RP, et al. Clinically significant macular edema in type I diabetes: incidence and risk factors. Ophthalmology 1995;102:1170–6.
12. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–9.
13. Aroca PR, Salvat M, Fernandez J, Mendez I. Risk factors for diffuse and focal macular edema. J Diabetes Complications 2004;18:211–5.
14. Williams R, Airey M, Baxter H, et al. Epidemiology of diabetic retinopathy and macular oedema: a systematic review. Eye 2004;18:963–83.
15. Miljanovic B, Glynn RJ, Nathan DM, et al. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. Diabetes 2004;53:2883–92.
16. Jaross N, Ryan P, Newland H. Incidence and progression of diabetic retinopathy in an Aboriginal Australian population: results from the Katherine Region Diabetic Retinopathy Study (KRDRS). Report no. 2. Clin Experiment Ophthalmol 2005; 33:26–33.
17. Leske MC, Wu SY, Hennis A, et al, Barbados Eye Study Group. Nine-year incidence of diabetic retinopathy in the Barbados Eye Studies. Arch Ophthalmol 2006;124:250–5.
18. Rossing P. The changing epidemiology of diabetic microangiopathy in type 1 diabetes. Diabetologia 2005;48:1439–44.
19. Chase HP, Lockspeiser T, Peery B, et al. The impact of the Diabetes Control and Complications Trial and Humalog insulin on glycohemoglobin levels and severe hypoglycemia in type 1 diabetes. Diabetes Care 2001;24:430–4.
20. Hovind P, Tarnow L, Rossing K, et al. Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes. Diabetes Care 2003;26:1258–64.
21. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? Diabetes Care 2008;31:81–6.
22. Klein R, Klein BE, Moss SE, et al. Prevalence of diabetes mellitus in southern Wisconsin. Am J Epidemiol 1984;119: 54–61.
23. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1984;102:520–6.
24. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984;102:527–32.
25. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1989;107:237–43.
26. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. Arch Ophthalmol 1994;112:1217–28.
27. Klein BE, Klein R, McBride PE, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Intern Med 2004;164:1917–24.
28. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XXII. The twenty-five-year progression of retinopathy with persons with type 1 diabetes. Ophthalmology 2008;115:1859–1868.
29. Hypertension Detection and Follow-Up Program Cooperative Group. The Hypertension Detection and Follow-Up Program. Prev Med 1976;5:207–15.
30. Early Treatment of Diabetic Retinopathy Study Research Group (ETDRS). Manual of Operations. Springfield, VA: National Technical Information Service; 1985;101–19. Accession no. PB85–223006.
31. Early Treatment Diabetic of Retinopathy Study Research Group. Manual of Operations. Springfield, VA: National Technical Information Service; 1985;207–43. Accession no. PB85–223006.
32. Moss SE, Klein R, Klein BE, et al. Methodologic considerations in measuring glycosylated hemoglobin in epidemiologic studies. J Clin Epidemiol 1988;41:645–9.
33. Klein R, Moss S. A comparison of the study populations in the Diabetes Control and Complications Trial and the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Intern Med 1995;155:745–54.
34. Klein R, Klein BE, Magli YL, et al. An alternative method of grading diabetic retinopathy. Ophthalmology 1986;93: 1183–7.
35. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus

photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 1991; 98(suppl):786–806.
36. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Ophthalmology 1991; 98(suppl):823–33.
37. Klein BE, Davis MD, Segal P, et al. Diabetic retinopathy: assessment of severity and progression. Ophthalmology 1984; 91:10–7.
38. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695–706.
39. Allison PD. Estimating Cox regression Model with PROC PHREG. In: Whatley J, ed. Survival Analysis using the SAS System: A Practical Guide. Cary, NC: SAS Institute Inc.; 1995;138–50.
40. Hirai FE, Knudtson MD, Klein BE, Klein R. Clinically significant macular edema and survival in type 1 and type 2 diabetes. Am J Ophthalmol 2008;145:700–6.
41. Roy MS, Affouf M. Six-year progression of retinopathy and associated risk factors in African American patients with type 1 diabetes mellitus: the New Jersey 725. Arch Ophthalmol 2006;124:1297–306.
42. West KM, Erdreich LJ, Stober JA. A detailed study of risk factors for retinopathy and nephropathy in diabetes. Diabetes 1980;29:501–8.
43. Knuiman MW, Welborn TA, McCann VJ, et al. Prevalence of diabetic complications in relation to risk factors. Diabetes 1986;35:1332–9.
44. Jerneld B. Prevalence of diabetic retinopathy: a population study from the Swedish island of Gotland. Acta Ophthalmol Suppl 1988;188:3–32.
45. Kostraba JN, Klein R, Dorman JS, et al. The Epidemiology of Diabetes Complications Study. IV. Correlates of diabetic background and proliferative retinopathy. Am J Epidemiol 1991;133:381–91.
46. Cruickshanks KJ, Ritter LL, Klein R, Moss SE. The association of microalbuminuria with diabetic retinopathy: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Ophthalmology 1993;100:862–7.
47. Klein R, Moss SE, Klein BE. Is gross proteinuria a risk factor for the incidence of proliferative diabetic retinopathy? Ophthalmology 1993;100:1140–6.
48. Romero P, Baget M, Mendez I, et al. Diabetic macular edema and its relationship to renal microangiopathy: a sample of type I diabetes mellitus patients in a 15-year follow-up study. J Diabetes Complications 2007;21:172–80.
49. Goldsmith JR, Landaw SA. Carbon monoxide and human health. Science 1968;162:1352–9.
50. Hawkins RI. Smoking, platelets and thrombosis. Nature 1972; 236:450–2.
51. Yanbaeva DG, Dentener MA, Creutzberg EC, et al. Systemic effects of smoking. Chest 2007;131:1557–66.
52. Adamis AP. Is diabetic retinopathy an inflammatory disease? Br J Ophthalmol 2002;86:363–5.
53. Klein R, Klein BE, Davis MD. Is cigarette smoking associated with diabetic retinopathy? Am J Epidemiol 1983;118:228–38.
54. Moss SE, Klein R, Klein BE. Association of cigarette smoking with diabetic retinopathy. Diabetes Care 1991;14:119–26.
55. Moss SE, Klein R, Klein BE. Cigarette smoking and ten-year progression of diabetic retinopathy. Ophthalmology 1996;103: 1438–42.

Footnotes and Financial Disclosures

Originally received: July 9, 2008.
Final revision: September 17, 2008.
Accepted: October 13, 2008.
Available online: January 22, 2009. Manuscript no. 2008-826.

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This research is supported by National Institutes of Health grant EY03083 and EY016379 (Ronald Klein, MD, MPH, Barbara E.K. Klein, MD, MPH) and, in part, by the Research to Prevent Blindness (R. Klein and BEK Klein, Senior Scientific Investigator Awards), New York, New York. The National Eye Institute provided funding for the entire study including collection and analyses and of data; RPB provided further additional support for data analyses.

Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by National Institutes of Health grant EY03083 and EY016379 (Ronald Klein, MD, MPH, Barbara E.K. Klein, MD, MPH) and, in part, by the Research to Prevent Blindness (R. Klein and BEK Klein, Senior Scientific Investigator Awards), New York, New York. The National Eye Institute provided funding for the entire study including collection and analyses and of data; RPB provided further additional support for data analyses.

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