The 25-Year Incidence of Visual Impairment in Type 1 Diabetes Mellitus

The Wisconsin Epidemiologic Study of Diabetic Retinopathy

Ronald Klein, MD, MPH,[1] Kristine E. Lee, MS,[1] Ronald E. Gangnon, PhD,[2] Barbara E. K. Klein, MD, MPH[1]

Objective: To examine the 25-year cumulative incidence of visual impairment (VI) and its relation to various risk factors.

Design: Population-based study.

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

Methods: Best-corrected visual acuity (VA) was measured using a modification of the Early Treatment Diabetic Retinopathy Study protocol. Visual impairment and severe VI were defined as best-corrected VA in the better eye of 20/40 or worse and 20/200 or worse, respectively.

Main Outcome Measures: Incidence of VI.

Results: The 25-year cumulative incidences of any VI and severe VI (accounting for competing risk of death) were 13% and 3%, respectively. Multivariate models showed increased risk of VI was associated (hazard ratio, 95% confidence interval, and *P* value) with more severe baseline retinopathy (1.14 per 1-step increase in retinopathy level; 1.03–1.27; $P = 0.01$), presence of cataract (2.49 versus absence; 1.53–4.04; $P<0.001$), higher glycosylated hemoglobin (1.28 per 1%; 1.16–1.42; $P<0.001$), presence of hypertension (1.72 versus absence; 1.05–2.83; $P = 0.03$), and currently smoking (vs. never smoked, 1.63; 1.01–2.61; $P = 0.04$), but not proteinuria.

Conclusions: These data show that the 25-year cumulative incidence of VI is related to modifiable risk factors and, therefore, that VI may be reduced by better glycemic and blood pressure control and avoidance of smoking.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2010;117:63–70 © 2010 by the American Academy of Ophthalmology.

Diabetic retinopathy (DR) is an important cause of visual impairment (VI), especially in persons 25 to 65 years of age.[1–4] Although epidemiologic studies have described the incidence of VI and its relationships to various risk factors, many of these studies have been in persons with type 2 diabetes, and few have examined these relationships over a long period.[5–14] This report extends previous observations by describing the 25-year cumulative incidence of any and severe VI and the doubling of the visual angle in a large cohort of persons with type 1 diabetes mellitus (T1DM) participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).[5,7,11]

Patients and Methods

Case identification methods and descriptions of the population have appeared in previous reports.[5,7,11,15–21] Briefly, the study area consisted of 11 counties in southern Wisconsin. From July 1, 1979, through June 30, 1980, 10 135 persons with diabetes were identified in the practices of 452 of 457 primary care physicians in the area. A 2-part sample of 2990 of these persons was invited to participate in the baseline examination from 1980 through 1982. The first part consisted of the entire population of persons taking insulin who were diagnosed as having diabetes before 30 years of age (n = 1210), and the second part consisted of a probability sample of persons who were diagnosed as having diabetes at or after 30 years of age (n = 1780).[15–22] Based on C-peptide testing, the first group is referred to as T1DM and analyses are limited to this group. Surviving younger-onset persons were invited to participate in follow-up examinations from 1984 through 1986, 1990 through 1992, 1995 through 1996, 2000 through 2002, and 2005 through 2007.[17–21] Differences in baseline characteristics among those who participated in a follow-up examination and those who did not have been presented elsewhere.[17–21]

All examinations followed a similar protocol, which 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 examination consisted of obtaining informed signed consent, measuring blood pressure,[23] measuring refractive error, determining best-corrected visual acuity (VA) for distance using a modified Early Treatment Diabetic Retinopathy Study protocol in which the charts were

ISSN 0161-6420/10/$–see front matter
doi:10.1016/j.ophtha.2009.06.051

reduced in size for a 2-m distance,[24] dilating the pupils, administering a medical history questionnaire, performing a slit-lamp examination, performing an ophthalmoscopic examination, obtaining stereoscopic color fundus photographs of 7 standard fields,[25] determining urine protein level, and determining blood glucose and glycosylated hemoglobin (HbA1) levels. Because the 2000 through 2002 examination was focused primarily on cardiovascular disease, measurements of refractive error and VA, dilation of pupils, and fundus photography were not completed at this examination.

For each eye, the best-corrected VA was recorded as the number of letters read correctly from 0 (20/250) to 70 (20/10).[16] For eyes with VA worse than 20/250, 1 of 6 levels of VA was recorded: 20/320, 20/400, 20/800, hand movements, light perception, and no light perception. The participant's VA was defined as the VA in the better eye. In this study, severe VI was defined as a VA of 20/200 or less in the better eye. Any VI is defined as a VA of 20/40 or less in the better eye. A doubling of the visual angle is defined as a loss of 15 letters (i.e., a change from 55 to 40 letters corresponds to a visual acuity change from 20/20 to 20/40). Persons with a VA of no light perception at baseline were not at risk for doubling of the visual angle. For analyses with demographic and systemic factors, this was determined for the better eye. For analyses with ocular factors, right and left eyes were analyzed separately.

To determine the severity of retinopathy in each eye, all fundus photographs were graded using a modification of the Early Treatment Diabetic Retinopathy Study classification scheme.[18,25] Briefly, level 10 represents no retinopathy, levels 21 through 53 represent nonproliferative retinopathy of increasing severity, and levels 60 through 85 represent proliferative retinopathy of increasing severity. Macular edema also was determined from the fundus photographs as described previously.[26] Macular edema was considered present if any area of the retina within 1 disc diameter from the center of the macula was thickened or if there was a prior history of macular edema with evidence of photocoagulation treatment consistent with it. Panretinal photocoagulation, focal/grid photocoagulation, or both, were determined by grading of fundus photographs. Cataract status (cortical, nuclear, and posterior subcapsular) was ascertained at the slit lamp. Glaucoma was based on history of glaucoma and treatment with intraocular pressure-lowering medications.

Current age was defined as the age at the time of the baseline examination. Duration of younger-onset diabetes was the interval between diagnosis of diabetes and the specific examination. Age at diagnosis was obtained from physician's chart. Glycemic control was measured by HbA1 using a microcolumn technique.[27,28] Hypertension was defined as a mean systolic blood pressure of 160 mmHg or more, a mean diastolic blood pressure of 95 mmHg or more, or both, or a history of antihypertensive medication at the time of examination in individuals 25 years of age or older or a mean systolic blood pressure of 140 mmHg or more, a mean diastolic blood pressure of 90 mmHg or more, a history of antihypertensive medication at the time of examination, or a combination thereof in younger persons. Urine samples were collected and tested for gross proteinuria by means of a reagent strip (Labstix; Ames, Elkhart, IN). Urine protein was defined as absent ($<$0.30 g/1) or present ($\geq$0.30/g/1). A subject was classified as a nonsmoker if he or she had smoked fewer than 100 cigarettes in his or her lifetime, a former smoker if he or she had smoked more than this number but had stopped smoking before the baseline examination, and a current smoker if he or she had not stopped. Pack-years smoked was defined as the number of packs of cigarettes (20 cigarettes/pack) smoked daily times the number of years smoked. Body mass index was defined as body weight (kg)/height(m^2).

Statistical Analysis

SAS software version 9 (SAS Inc., Cary, NC) was used for analyzing the data. Data were structured such that each participant contributed data for every examination VA was measured until they obtained the VI outcome or were otherwise censored. Cumulative 25-year incidence of visual impairment and of doubling of the visual angle were calculated considering competing risk of death.[29] This is an adaptation of the Kaplan-Meier product limit method that considers only those who were alive and free of disease to be at risk for failure rather than the traditional approach that treats those censored because of death as still being at risk for failure. In the competing event approach, both death and the event of interest are included in calculating the probability of surviving up to time t. There were a total of 367 subjects who died (195 of these are considered competing events), 64 (42 competing) from the baseline examination to the start of the first follow-up, 86 (48 competing) from the first follow-up examination to the start of the second follow-up, 64 (29 competing) from the second follow-up examination to the start of the third follow-up examination, and 153 (76 competing) from the third follow-up examination to the start of the fifth follow-up examination. Estimated incidence and rates of progression between examinations were converted to average annual rates using the formula: $1–(1–p_n)1/n$, where n is the number of years between examinations and p_n is the cumulative rate between examinations.

For multivariate analyses, generalized linear models were used for the binary outcomes (incidence of VI and doubling of the visual angle during the examination interval) using the complementary log-log link function to estimate underlying continuous-time proportional hazard models 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 a piecewise constant within 5-year bands of diabetes duration starting at 20 years and continuing to more than 40 years. Hazard ratio estimates were calculated by exponentiation of estimated coefficients. The PROC NLMIXED of SAS software version 9.1 (SAS Institute) was used for these analyses. Three sets of models were considered: (1) models including only baseline characteristics; (2) models including baseline characteristics without retinopathy severity included; and (3) models using time-varying covariates updated at each follow-up examination (i.e., for each interval in which a subject participated, the values of the risk factors at the beginning of the interval were used).[30]

Results

Nine hundred ninety-five participants contributed 3719 participant-visits for the analysis of the incidence of VI. Characteristics of the cohort have been described in detail elsewhere.[5,7,11,15–21] For the 482 participants in the 2005 through 2007 examination, the baseline values of characteristics were: mean age, 24.9$\pm$9.3 years; mean duration of diabetes, 10.7$\pm$7.1 years; mean HbA1, 10.5$\pm$2.0%; mean systolic and diastolic blood pressures, 118.4$\pm$14.0 mmHg and 77.0$\pm$10.6 mmHg, respectively; mean body mass index, 23.1$\pm$3.8 kg/m^2; and mean pack-years smoked (among those 18 years of age and older [n = 369]), 4.0$\pm$10.0. At baseline, 49.8% of the cohort was male; 12.3% had a history of hypertension; 12.3% had proteinuria; 24.1% (of those 18 years of age and older) were current smokers; 2.3% were visually impaired, of whom 9% were severely impaired; 14.0% had a cataract; 0.8% had glaucoma; 8.3% had proliferative DR; 5.3% had macular edema, of whom 60% had clinically significant macular edema; 5.2% had panretinal photocoagulation treatment; and 0.2% had focal or grid photocoagulation treatment for macular edema.

The mean decrease in the number of letters read correctly over the 25-year period of the study was similar in the right eye (−6.7±18.9) and left eye (−7.6±18.0; $P = 0.46$). Those who had a shorter duration of diabetes lost fewer letters during the 25-year period than those who had a longer duration of diabetes at baseline (Fig 1), but this trend was not statistically significant. For right eyes, it varied from −3.87±17.0 letters in people with less than a 5 year duration of diabetes to −9.29±24.6 letters in people with a duration of diabetes of 15 years or more at baseline. Similar relations were found for left eyes (data not shown). There was a statistically significant inverse relationship between the mean change in the number of letters read correctly between examinations and severity of DR such that those with no DR at baseline lost fewer letters during the 25-year period than those with more severe retinopathy (Fig 2). The mean decrease in the number of letters read correctly varied from −4.6±16.3 letters in right eyes with no DR at baseline to −20.5±42.1 letters in right eyes with proliferative DR present at baseline. Similar relations were found for left eyes (data not shown).

Factors Associated with the Cumulative Incidence of Visual Impairment

The 25-year cumulative incidence of any VI and severe VI in the better eye in the population accounting for the competing risk of death was 13% (95% confidence interval [CI], 11%–16%) and 3% (95% CI, 1%–4%), respectively (Table 1). For right eyes, the 25-year cumulative incidence of any VI and severe VI in the population was 22% (95% CI, 19%–25%) and 6% (95% CI, 4%–7%), respectively, whereas for left eyes, it was 21% (95% CI, 18%–24%) and 6% (95% CI, 4%–8%), respectively. Using the World Health Organization definitions, the 25-year cumulative incidence of moderately severe visual impairment (best-corrected VA in the better eye of ≤20/80 and >20/200) and blindness (best-corrected VA in the better eye of <20/400) was 3.0% and 1.2%, respectively.

Cumulative incidence of VI and severe VI in the better eye and competing risk of death increased with age and duration of diabetes (Table 1). The estimates of the annual incidence of any and severe VI over the 4 study intervals are presented in Figure 3.

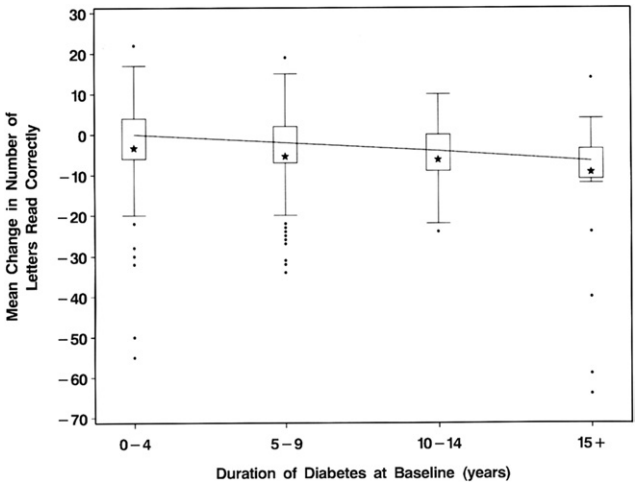

Figure 1. Graph showing the 25-year change in the mean number of letters correctly read in right eyes by duration of diabetes at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Box extends from twenty-fifth to the seventy-fifth percentiles with line at median. Mean change indicated by star.

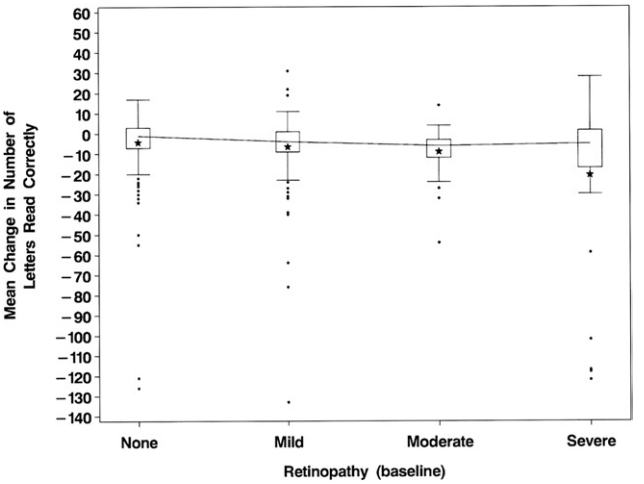

Figure 2. Graph showing the 25-year change in the mean number of letters correctly read in right eyes by severity of diabetic retinopathy at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Box extends from the twenty-fifth to the seventy-fifth percentiles with line at median. Mean change indicated by star.

Because the length of the interval varies over the study, the width of the bars in the figure reflects the length of the interval. The annualized estimates are similar for any VI except for the last period, where it was markedly lower; a less consistent temporal pattern was found for severe VI. To evaluate whether this drop in the last period is real or because of the different interval length, the annualized incidence was examined between the 1980 through 1982 and 1990 through 1992 examinations. This annualized rate of 0.65 (not shown) for any VI is still higher than the comparable interval 1995 through 1996 to 2005 through 2007 annualized rate of 0.28.

In univariate analyses, having a higher HbA1 level, higher systolic or diastolic blood pressure, hypertension, gross proteinuria, being a current smoker, having more pack-years smoked while having diabetes, having more severe DR, having cataract, and having macular edema at baseline were associated significantly with the incidence of any VI (Table 2). Being male, having glaucoma, or having a greater BMI were not associated with the incidence of VI (Table 2). Similar analyses were not carried out for severe VI because of its low incidence.

Multivariate analyses showed that while controlling for duration of diabetes, increased risk of VI was associated with more severe baseline DR, cataract presence, higher HbA1, presence of hypertension, and currently smoking (vs. never smoked; Table 2), but not proteinuria, a history of glaucoma, or macular edema (data not shown). When DR severity was not entered into the model, presence of gross proteinuria at baseline (hazard ratio [HR], 1.74; 95% CI, 1.07–2.84; $P = 0.03$) was associated significantly and macular edema (HR, 1.67; 95% CI, 0.97–2.88; $P = 0.07$) was associated marginally with the incidence of VI.

Time-varying covariate analyses were consistent with analyses using only baseline measurements with retinopathy in the model, except that the associations of proteinuria with incident VI was statistically significant (HR, 1.80; 95% CI, 1.14–2.84; $P = 0.01$), whereas hypertension and smoking status with incident VI no longer were statistically significant (data not shown).

Among the 160 right eyes in which any VI developed, 75% had proliferative diabetic retinopathy, 17% had clinically significant macular edema, 13% had glaucoma, and 55% had cataract at a previous examination or at the examination at which the VI was

Table 1. Twenty-Five Year Cumulative Incidence of Any and Severe Visual Impairment and Doubling of the Visual Angle in Better Eye by Age and Duration of Diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy

	Incidence of Any Visual Impairment				Incidence of Doubling of Visual Angle				Incidence of Severe Visual Impairment			
			Cumulative Incidence (%)				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	No. at Risk	No. Events	Event	Risk of Dying before Event
All Groups (yrs)	874	105	13.3	27.3	939	126	15.1	30.3	920	21	2.5	36.6
0–9	24	0	0.0	0.0	25	0	0.0	0.0	25	0	0.0	0.0
10–14	77	3	5.5	13.7	80	4	7.6	13.3	80	1	2.3	15.6
15–19	145	5	3.8	20.6	147	10	7.8	19.1	147	1	1.0	22.1
20–24	145	16	13.0	11.0	153	26	19.9	11.8	153	5	3.4	16.1
25–29	129	18	14.7	22.2	136	19	14.8	24.7	135	4	3.2	31.8
30–34	131	16	14.7	28.7	140	14	11.8	33.9	137	0	0.0	36.0
35+	223	47	21.9	48.8	258	53	21.6	54.0	243	10	4.2	67.0
Diabetes duration (yrs)												
0–2	74	5	8.5	8.8	75	6	10.6	8.7	75	0	0.0	14.6
3–4	82	5	9.1	14.1	83	6	10.1	13.9	83	1	1.6	14.1
5–9	232	15	8.0	16.3	237	23	12.4	15.3	237	1	0.6	18.3
10–14	159	14	9.3	18.5	164	21	13.8	19.7	164	3	1.9	24.2
15–19	114	18	16.7	29.0	130	23	18.5	32.2	127	8	6.8	39.8
20–24	73	11	16.2	44.2	81	13	17.4	47.3	78	5	6.9	53.7
25–29	63	9	15.4	60.8	76	12	16.7	59.6	70	3	4.3	69.4
30+	77	28	37.2	55.7	93	22	24.5	69.6	86	0	0.0	90.9

first detected. Similar findings were found in left eyes (data not shown).

Factors Associated with the Cumulative Incidence of Doubling of the Visual Angle

The 25-year cumulative incidence of doubling of the visual angle in the population accounting for the competing risk of death was 15% (95% CI, 13%–18%; Table 1). Cumulative incidence of doubling of the visual angle increased with age and duration of diabetes (Table 1).

In univariate analyses, higher HbA1 level, higher systolic or diastolic blood pressure, hypertension, gross proteinuria, having more pack-years smoked, having more severe DR, having cataract, having a history of glaucoma, and having macular edema at baseline were associated significantly with the incidence of doubling of the visual angle (Table 3). Being male or having greater body mass index was not associated with incidence of doubling of the visual angle (Table 3).

Multivariate analyses showed that while controlling for duration of diabetes, increased risk of doubling of the visual angle was associated with cataract presence, history of glaucoma, higher HbA1, and proteinuria (Table 3). There were borderline associations with more severe baseline retinopathy and current smoking (vs. never smoked; Table 3), but not hypertension or macular edema (data not shown). When DR severity was not entered into the model, there was a borderline association between presence of hypertension (HR, 1.53; 95% CI, 0.96–2.43; $P = 0.07$) and the incidence of doubling of the visual angle.

Time-varying covariate analyses were consistent with analyses using only baseline measurements with retinopathy in the model, except that the association of macular edema with incident VI was of borderline statistical significance (HR, 1.52; 95% CI, 1.00–2.31; $P = 0.05$), whereas history of glaucoma with incident VI no longer was statistically significant (data not shown).

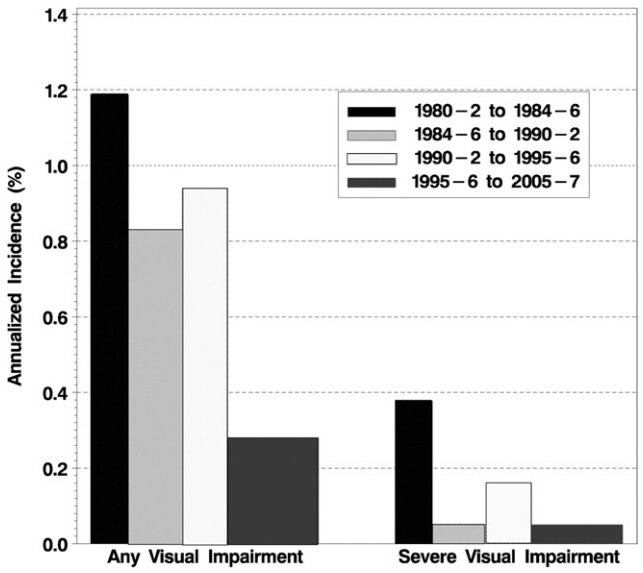

Figure 3. Bar graph showing the estimated annual rates for incidence of any and severe visual impairment for 4 periods of the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Width of bar corresponds to length of period.

Discussion

The data reported herein provide unique population-based information regarding the 25-year cumulative rates of VI and change in vision and their relationships to retinopathy severity, cataract, glycemia, blood pressure, smoking, and other factors in persons with T1DM. The overall 25-year incidence of any VI (13%) and doubling of the visual angle

Table 2. Associations with the 25-Year Cumulative Incidence of Any Visual Impairment in the Wisconsin Epidemiologic Study of Diabetic Retinopathy*

		Controlling Only for Duration of Diabetes			Multivariate*		
Risk Variable	**Level**	*Hazard Ratio*	*95% Confidence Interval*	P *Value*	*Hazard Ratio*	*95% Confidence Interval*	P *Value*
Gender	Male	1.10	0.75–1.61	0.62			
Glycosylated hemoglobin A_1	Per 1%	1.33	1.21–1.46	<0.001	1.28	1.16–1.42	<0.001
Glycosylated hemoglobin A_1 quartiles	9.5–10.5 vs. <9.5%	1.61	0.80–3.23	0.18			
	10.6–12.0 vs. <9.5%	1.83	0.93–3.60	0.08			
	12.1–19.5 vs. <9.5%	4.33	2.32–8.07	<0.001			
Proteinuria	Present	2.90	1.92–4.37	<0.001	NS		
Retinopathy severity	21 vs. 10	1.62	0.77–3.44	0.21			
	31–37 vs. 10	1.86	0.92–3.78	0.08			
	43–53 vs. 10	3.19	1.50–6.77	0.003			
	60+ vs. 10	8.26	4.22–16.17	<0.001			
15-level retinopathy severity	Per 2 steps	1.35	1.25–1.46	<0.001	1.14	1.03–1.27	0.01
Macular edema	Present	2.66	1.61–4.39	<0.001	NS		
Cataract	Present	3.68	2.37–5.70	<0.001	2.49	1.53–4.04	<0.001
History of glaucoma	Present	3.92	0.96–16.03	0.06	NS		
Systolic blood pressure	Per 10 mmHg	1.40	1.27–1.55	<0.001			
Diastolic blood pressure	Per 10 mmHg	1.53	1.27–1.83	<0.001			
Hypertension	Present	2.74	1.82–4.12	<0.001	1.72	1.05–2.83	0.03
Smoking history†	Past vs. never	1.24	0.72–2.11	0.44	NS		
	Current vs. never	1.69	1.09–2.61	0.02	1.63	1.01–2.61	0.04
Pack years smoked†	<5 pack-years	0.90	0.49–1.65	0.73			
	5–14 pack-years vs. never	1.26	0.68–2.31	0.46			
	≥15 pack-years vs. never	2.26	1.36–3.74	0.002			
Pack year smoked	Per 1 SD	1.38	1.17–1.64	<0.001			
Body mass index	Per 1 SD	1.08	0.89–1.30	0.435			

NS = not statistically significant; SD = standard deviation.
*All variables included in a single model. Use of hypertension to represent blood pressure rows, smoking history instead of pack years and continuous rather than categorical for retinopathy severity and glycosylated hemoglobin level. Missing rows indicate that variable was not significant.
†Restricted to those 18 years and older.

(15%) were high, and the strongest most consistent relationships were with glycemia, retinopathy severity, cataract, and smoking.

There are few other population-based cohorts of persons with T1DM with a similar length of follow-up with which these data can be compared. One is the 25-year follow-up of persons with T1DM living in Fyn County, Denmark (Invest Ophthalmol Vis Sci 49:E-abstract 1161, 2008), which reports a 25-year incidence of severe VI of 7.5% that is higher than the 3% found in the WESDR cohort. The higher incidence in the Danish cohort may be the result of the identification of their subjects with incident severe VI through blindness registries, whereas in the WESDR, incident severe VI was identified only at the time of each follow-up examination. It is possible that WESDR subjects with incident severe VI, who are at a higher risk of death, were less likely to be identified if they died before coming in for a follow-up examination. In addition, cumulative incidences taking into account competing risk of death are reported in the WESDR whereas in the Fyn County study, severe VI did not take competing risk of death into account. In a 20-year follow-up of a cohort which was diagnosed to have diabetes in Rochester, Minnesota, from 1945 through 1969, the cumulative incidence of severe VI was 8.2%.[31] However, the incidence of severe VI was not reported by type of diabetes in that study. Most other studies have reported severe VI in persons with T1DM over shorter periods.[6,8,32] Comparisons of visual loss among studies must be made with care because of differences in the methods used to ascertain visual loss and the periods in time in which the cohorts were studied.

Based on these findings, it is estimated that over a 25-year study period, of the 515 000 to 1.3 million Americans thought at present to have T1DM, VI will develop in approximately 66 950 to 169 000, in whom 15 400 to 39 000 severe VI will develop (NIDDK Clearing House; available at: http://www.medhelp.org/NIHlib/GF-254.html#four; accessed December 26, 2008). The decline in annualized incidence of VI between the 1995 through 1996 and 2005 through 2006 examinations from earlier periods suggests the possibility that applying these figures to persons who currently have T1DM may overestimate the number of persons in whom VI will develop over the next 25 years. This information on declining incidence of VI 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 VI in persons with T1DM, there may be a need for

Table 3. Associations with the 25-Year Cumulative Incidence of Controlling Only for Duration of Diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy*

		Doubling of Visual Angle			Multivariate*		
Risk Variable	**Level**	*Hazard Ratio*	*95% Confidence Interval*	*P Value*	*Hazard Ratio*	*95% Confidence Interval*	*P Value*
Gender	Male	1.01	0.72–1.40	0.98			
Glycosylated hemoglobin A_1	Per 1%	1.29	1.20–1.40	<0.001	1.27	1.16–1.38	<0.001
Glycosylated hemoglobin A_1 quartiles	9.5–10.5 vs. <9.5%	2.16	1.22–3.84	0.01			
	10.6–12.0 vs. <9.5%	1.93	1.09–3.43	0.02			
	12.1–19.5 vs. <9.5%	3.56	2.07–6.11	<0.001			
Proteinuria	Present	3.24	2.26–4.65	<0.001	1.84	1.15–2.96	0.01
Retinopathy severity	21 vs. 10	1.65	0.89–3.07	0.11			
	31–37 vs. 10	1.80	1.00–3.26	0.05			
	43–53 vs. 10	3.15	1.67–5.93	<0.001			
	60+ vs. 10	6.81	3.88–11.95	<0.001			
15-level retinopathy severity	Per 2 steps	1.31	1.23–1.40	<0.001	1.10	1.00–1.21	0.05
Macular edema	Present	2.20	1.36–3.54	<0.001	NS		
Cataract	Present	3.03	2.06–4.48	<0.001	1.72	1.10–2.70	0.02
History of glaucoma	Present	7.77	3.60–16.80	<0.001	5.56	1.23–25.16	0.03
Systolic blood pressure	Per 10 mmHg	1.30	1.20–1.42	<0.001			
Diastolic blood pressure	Per 10 mmHg	1.41	1.21–1.65	<0.001			
Hypertension	Present	2.61	1.82–3.75	<0.001		NS	
Smoking history†	Past vs. never	1.17	0.72–1.91	0.53			
	Current vs. never	1.60	1.09–2.34	0.02	1.48	0.97–2.27	0.07
Pack years smoked†	<5 pack-years	0.98	0.59–1.64	0.95			
	5–14 pack-years vs. never	1.34	0.79–2.28	0.28			
	≥15 pack-years vs. never	2.05	1.28–3.27	0.003			
Pack-year smoked	Per 1 SD	1.37	1.17–1.60	<0.001			
Body mass index	Per 1 SD	1.13	0.96–1.32	0.14			

NS = not statistically significant; SD = standard deviation.
*All variables included in a single model. Use of hypertension to represent blood pressure rows, smoking history instead of pack years and continuous rather than categorical for retinopathy severity and glycosylated hemoglobin level. Missing rows indicate that variable was not significant.
†Restricted to those 18 years of age and older.

fewer health care resources to support and rehabilitate these individuals.

Visual impairment was associated strongly with the severity of retinopathy and the presence of macular edema at baseline. Compared with persons without DR at baseline, persons with proliferative DR had an 8-fold higher risk of developing VI and a 29-fold higher risk of developing severe VI over the 25-year period (Klein R, unpublished data, 2008). Using time-varying covariates showed that the risk of incident VI when proliferative DR or macular edema was present seemed to be similar in each period. This was despite a higher proportion of eyes with proliferative DR and eyes with clinically significant macular edema having undergone photocoagulation treatment in more recent periods of observation compared with earlier periods (Klein R, unpublished data, 2008).

Glycemic control at baseline and throughout the study was related strongly to incidence of VI. This is consistent with earlier findings and with findings from other studies.[5,7,11,32] While controlling for other factors, each percentage-point increase in the HbA1 level at baseline in this study was associated with a 28% increase in the 25-year incidence of any VI, whereas each percentage-point increase in the HbA1 level at baseline was associated with a 27% increase in doubling of the visual angle in this study. Similar results were found in models that updated HbA1 and changes in it between examinations at each interval of evaluation.

At the time of the 14-year follow-up of the cohort, a univariate association was reported of pack-years smoked after being diagnosed with diabetes that no longer was statistically significant after controlling for other risk factors.[11] With the longer follow-up, while controlling for DR severity, glycemic control, and other risk factors, current smoking at baseline was found to increase the risk of incident VI by 63%. Smoking has never been found to be associated with the incidence and progression of DR in the WESDR.[19] Although smoking may not affect severity of retinopathy, its hypoxic effect independently may have an affect on vision.[33] It also is possible that smoking may have resulted in an increased incidence of cataract, explaining, in part, this relationship. This relationship of smoking to cataract has been found in the general population.[34] However, the association remained, although attenuated, when controlling for cataract status.

The relation of hypertension to the higher incidence of VI was not unexpected. In the WESDR, presence of hypertension was associated with a 73% increase in the risk of incident proliferative DR.[21] However, while a beneficial effect of lowering blood pressure on progression of DR and reduction in loss of vision has been shown in persons with type 2 diabetes, randomized controlled clinical trials have not shown a similar effect in persons with T1DM.[35–39] Regardless of the effect of blood pressure on visual impairment, intensive control of blood pressure has been shown to

be beneficial in reducing morbidity (myocardial infarction, stroke, and nephropathy) and mortality.

There are many strengths of the study, including a large cohort with a broad distribution of severity of DR at baseline, a low refusal rate, and use of standardized protocols of measurement, which included objective recording of VI using Early Treatment Diabetic Retinopathy Study protocols. However, caution should be observed when interpreting the findings from this study. Mortality may affect the relation of risk factors to incidence of end points. Because HbA1, blood pressure, gross proteinuria, and retinopathy severity level are associated significantly with incident VI and decreased survival,[40] it is likely that the effect of death diminishes the strength of these relationships.

In summary, these data suggest that better glycemic control and, to a lesser extent, not smoking and blood pressure control may be beneficial in reducing the incidence of VI in people with T1DM. Decreasing estimates of annualized incidence of VI in the cohort may reflect changes in management of DR. These data are important in planning for future needs for care and associated costs in persons with T1DM in whom VI develops.

References

1. Buch H, Vinding T, Nielsen NV. Prevalence and causes of visual impairment according to World Health Organization and United States criteria in an aged, urban Scandinavian population: the Copenhagen City Eye Study. Ophthalmology 2001;108:2347–57.
2. Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. JAMA 2003;290: 2057–60.
3. Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477–85.
4. Zhang X, Gregg EW, Cheng YJ, et al. Diabetes mellitus and visual impairment: National Health and Nutrition Examination Survey, 1999–2004. Arch Ophthalmol 2008;126:1421–7.
5. Moss SE, Klein R, Klein BE. The incidence of vision loss in a diabetic population. Ophthalmology 1988;95:1340–8.
6. Agardh E, Agardh CD, Hansson-Lundblad C. The five-year incidence of blindness after introducing a screening programme for early detection of treatable diabetic retinopathy. Diabet Med 1993;10:555–9.
7. Moss SE, Klein R, Klein BE. Ten-year incidence of visual loss in a diabetic population. Ophthalmology 1994;101:1061–70.
8. Henricsson M, Tyrberg M, Heijl A, Janzon L. Incidence of blindness and visual impairment in diabetic patients participating in an ophthalmological control and screening programme. Acta Ophthalmol Scand 1996;74:533–8.
9. Trautner C, Icks A, Haastert B, et al. Incidence of blindness in relation to diabetes: a population-based study. Diabetes Care 1997;20:1147–53.
10. Backlund LB, Algvere PV, Rosenqvist U. New blindness in diabetes reduced by more than one-third in Stockholm County. Diabet Med 1997;14:732–40.
11. Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. Ophthalmology 1998;105:998–1003.
12. Miki E, Lu M, Lee ET, et al, WHO Multinational Study Group. The incidence of visual impairment and its determinants in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001;44(suppl):S31–6.
13. Voutilainen-Kaunisto RM, Terasvirta ME, Uusitupa MI, Niskanen LK. Occurrence and predictors of retinopathy and visual acuity in Type 2 diabetic patients and control subjects: 10-year follow-up from the diagnosis. J Diabetes Complications 2001;15:24–33.
14. Kumar N, Goyder E, McKibbin M. The incidence of visual impairment due to diabetic retinopathy in Leeds. Eye 2006; 20:455–9.
15. 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.
16. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology 1984;91:1–9.
17. 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.
18. 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.
19. 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.
20. 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.
21. Klein R, Knudtson MD, Lee KE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII. The twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology 2008;115:1859–68.
22. 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.
23. Hypertension Detection and Follow-up Program Cooperative Group. The Hypertension Detection and Follow-up Program. Prev Med 1976;5:207–15.
24. Early Treatment Diabetic Retinopathy Study (ETDRS) Manual of Operations. Bethesda, MD: National Eye Inst.; 1985: 101–19. NTIS PB85-223006.
25. Diabetic Retinopathy Study Research Group. Report Number 7. A modification of the Airlie House classification of diabetic retinopathy. Invest Ophthalmol Vis Sci 1981;21: 210–26.
26. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: IV. Diabetic macular edema. Ophthalmology 1984;91:1464–74.
27. Moss SE, Klein R, Klein BE, et al. Methodologic considerations in measuring glycosylated hemoglobin in epidemiologic studies. J Clin Epidemiol 1988;41:645–9.
28. 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.
29. 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.

30. Parmar MK, Machin D. Survival Analysis: A Practical Approach. New York: Wiley; 1995:160–77.
31. Dwyer MS, Melton LJ III, Ballard DJ, et al. Incidence of diabetic retinopathy and blindness: a population-based study in Rochester, Minnesota. Diabetes Care 1985;8:316–22.
32. Lovestam-Adrian M, Agardh CD, Torffvit O, Agardh E. Diabetic retinopathy, visual acuity, and medical risk indicators: a continuous 10-year follow-up study in type 1 diabetic patients under routine care. J Diabetes Complications 2001;15: 287–94.
33. McFarland RA. The effects of exposure to small quantities of carbon monoxide on vision. Ann N Y Acad Sci 1970;174: 301–12.
34. Klein BE, Klein R, Linton KL, Franke T. Cigarette smoking and lens opacities: the Beaver Dam Eye Study. Am J Prev Med 1993;9:27–30.
35. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–13.
36. UK Prospective Diabetes Study (UKPDS) Group. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. Arch Ophthalmol 2004;122:1631–40.
37. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086–97.
38. Chaturvedi N, Sjolie AK, Stephenson JM, et al, EUCLID Study Group. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. Lancet 1998; 351:28–31.
39. Sjolie AK, Klein R, Porta M, et al, DIRECT Programme Study Group. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Lancet 2008;372:1385–93.
40. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Association of ocular disease and mortality in a diabetic population. Arch Ophthalmol 1999;117:1487–95.

Footnotes and Financial Disclosures

Originally received: February 16, 2009.
Final revision: May 1, 2009.
Accepted: June 22, 2009.
Available online: October 31, 2009. Manuscript no. 2009-220.

[1] Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

[2] Departments of Population Health Sciences and of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Financial Disclosure(s):
The author(s) have made the following disclosure(s):

Ronald Klein - Consultant - Astra-Zeneca, Lilly, and Pfizer.

The other authors do not have any financial disclosures.

Supported by the National Institutes of Health, Bethesda, Maryland (grant nos.: EY03083 and EY016379 [RK, BEK]); and, in part, by Research to Prevent Blindness, Inc., New York, New York (RK and BEKK, Senior Scientific Investigator Awards). The National Eye Institute provided funding for the entire study, including collection and analyses and of data; Research to Prevent Blindness provided further additional support for data analyses.

Correspondence:
Ronald Klein, MD, MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, 610 North Walnut Street, 417 WARF, Madison, WI 53726-2336. E-mail: kleinr@epi.ophth.wisc.edu.