

# Are Individuals With Diabetes Seeing Better?

## A Long-Term Epidemiological Perspective

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**D**iabetic retinopathy (DR) was the leading cause of severe visual impairment (VI) in subjects 25–64 years of age in the U.S. 30 to 40 years ago (1,2). At that time, severe VI (best corrected visual acuity of 20/200 or worse in the better eye) was 25 times as common in subjects with diabetes compared with those without diabetes. VI in subjects with diabetes resulted mainly from vitreous hemorrhage, tractional detachment of the macula due to proliferative diabetic retinopathy (PDR), and from macular edema involving the foveal area due to leakage from the breakdown of the blood-retinal barrier. Cataract and glaucoma also contributed to VI in individuals with diabetes.

Poor glycemic control was common in subjects with diabetes at that time (3,4). This was due, in part, to the fact that intensive appropriate insulin treatment was difficult to achieve. This was related to the technology that was available for monitoring glucose levels (self-monitoring of glycemic control was done by testing of spot urines; no glycosylated hemoglobin A1c was available) and to the way insulin was administered (no pump, treatment with one injection per day of a long-acting insulin). There was no definitive evidence that achieving good glycemic control would actually result in less DR; thus, there was a lack of consensus on optimal glucose levels among physicians caring for individuals with diabetes. Some clinicians believed that high blood glucose was less likely to result in the development of severe DR in subjects with type 2 diabetes than in those with type 1 diabetes (5). Blood pressure was also poorly controlled in individuals with diabetes at that time (3,4).

In 1972, the efficacy of photocoagulation had not yet been demonstrated to prevent visual loss due to PDR or macular edema. Vitrectomy, a surgical intervention to restore vision in eyes with vitreous hemorrhage or tractional detachments of the macula, was in its developmental stages.

The purpose of this article is to provide a historical epidemiological perspective showing the relation of changes in the management of diabetes and its retinal and visual complications to the changes in the incidence and progression of DR and VI over the past 30 years.

**Evidence of a relationship of hyperglycemia to DR.** In 1979, the relationship between hyperglycemia and the development of DR had not been resolved. Kelly M. West, in his 1978 textbook, *Epidemiology of Diabetes and Its Vascular Lesions*, wrote, “The extent to which the level of hyperglycemia determines the risk of retinopathy is not at all clear. This is the most important issue at hand and deserves high priority in epidemiologic research” (6). Baseline data (1980–1982) from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a cohort study of both type 1 and type 2 diabetes showed that less than 10% of individuals with diabetes achieved levels of glycemia (glycosylated hemoglobin A1c <7%) and blood pressure (<130/80 mmHg) considered adequate by today’s standards (Table 1) (3,4).

Epidemiological data from the WESDR and other cohort studies showed that glycemic control was strongly related to the incidence and progression of DR and that achieving glycemic control was beneficial at any time during the course of diabetes and at any level of severity of DR prior to the onset of PDR (7). There was no threshold level above normal at which the lowering of glycosylated hemoglobin levels was not associated with the lowering of risk of incidence or progression of DR. Moreover, for a given level of glycemia, the risk of retinopathy progressing or developing into PDR or clinically significant macular edema (CSME) (the thickening of the retina involving the fovea or a certain area threatening the fovea) was similar for both individuals with type 1 and type 2 diabetes. This provided evidence that glycemic control and not the type of diabetes was important in determining risk of progression of DR.

Two large randomized therapeutic trials of metabolic control, the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) (for type 1 and type 2 diabetes, respectively), provided evidence of the efficacy of intensive glycemic control (8,9). DCCT showed an approximate 76% reduction in the progression of retinopathy in the primary prevention cohort (subjects without DR at baseline) and a 54% reduction in the progression of DR in the secondary prevention cohort (subjects with mild to moderate nonproliferative diabetic retinopathy [NPDR] at baseline) in the intensive therapy group compared with the conventional therapy group after five years of follow-up. DCCT data suggested that if intensive therapy for the 120,000 subjects with type 1 diabetes in the U.S. who met DCCT criteria could maintain a hemoglobin A1c level of 7.2% for life, 920,000 years of sight would be gained (10). The long-term benefits of intensive treatment went well beyond its implementation and led investigators to suggest that “intensive treatment should be started as soon as is safely possible after the onset of type 1 diabetes and maintained thereafter, aiming for a practicable target HbA1c level of 7.0% or less” (11). However, achieving intensive glycemic control in the

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Received 29 December 2009 and accepted 19 May 2010.  
DOI: 10.2337/db09-1904

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TABLE 1  
 Characteristics of the Wisconsin Epidemiologic Study of Diabetic Retinopathy cohort in 1980–1982

Characteristic	Type 1 diabetic subjects		Type 2 diabetic subjects	
	All	≥15 years	All	≥15 years
Mean glycosylated hemoglobin A1c (%)	10.1	10.0	8.9	9.3
% with glycosylated A1c <7.0%	2.7	2.2	15.2	6.1
Prevalence of hypertension (systolic BP ≥130 and/or diastolic BP ≥80 mmHg and/or history of hypertension using antihypertensive medications) (%)	56.4	72.3	87.1	87.5
% on antihypertensive medications with controlled BP <130/80 mmHg	1.4	2.8	5.1	5.7
Prevalence of DR (%)	71.8	97.5	49.7	77.9
Prevalence of PDR (%)	22.8	48.5	5.7	14.5
Prevalence of clinically significant macular edema (%)	5.9	11.1	5.2	15.6
% of right eyes with PDR treated with PRP	53.9	55.6	38.9	46.9
% of right eyes with clinically significant macular edema treated with focal/grid photocoagulation	31.7	32.0	29.3	23.2
Prevalence of visual impairment (%)*	8.0	16.4	11.7	23.8
Prevalence of severe visual impairment (%)*	3.2	7.9	1.6	4.8

\*Visual impairment defined as best corrected visual acuity of 20/40 or worse in the better eye; severe visual impairment as best corrected visual acuity of 20/200 or worse in the better eye. BP, blood pressure; PRP, panretinal photocoagulation.

DCCT resulted in a two- to threefold increase in severe hypoglycemia in the intensive insulin treatment group compared with the conventional group.

The UKPDS showed the efficacy of intensive glycemic control in newly diagnosed type 2 diabetic individuals (9). There was a 21% reduction in the progression of DR and a 29% reduction in the need for laser photocoagulation in the intensive treatment group compared with the conventional treatment group after 12 years of follow-up. Both trials provided a basis for the American Diabetes Association (ADA) guidelines of a target level of glycosylated hemoglobin of 7.0% for individuals with diabetes.

**Evidence of a relationship of hypertension to DR.** Randomized clinical trial data have shown the efficacy of the tight control of blood pressure in reducing the progression of DR in subjects with type 2 diabetes (12,13). In the UKPDS, tight blood pressure control (defined as achieving blood pressure values <150/<85 mmHg) in subjects with type 2 diabetes resulted in a 34% reduction in the progression of DR and a 47% reduction in the decrease in visual acuity of three lines or more over 7½ years of follow-up compared with conventional control (defined as blood pressure values <180/<105 mmHg) (12). The reduction in the loss of vision was due mainly to a 42% reduction in the incidence of macular edema. In the UKPDS, the effects of blood pressure control were independent of those attributable to glycemic control. In the DIabetic REtinopathy Candesartan Trials (DIRECT), candesartan was associated with a statistically insignificant reduction in the progression of DR over a 4½ year period in subjects with type 2 diabetes who were normotensive or had controlled hypertension, as compared with those randomized to a placebo (14).

Three randomized controlled clinical trials, the EURODIAB (Epidemiology and Prevention of Diabetes project) Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID), the Renin-Angiotensin System Study (RASS), and the DIRECT Prevent-1, have shown that either ACE inhibition (ACE-I) or angiotensin receptor blocker (ARB) reduction was associated with the reduction in the progression of DR in normotensive type 1 diabetic subjects with no or very mild DR (15–17). In each of these trials, the effect was independent of blood pressure level. It remains uncertain and speculative whether there are pleiotropic drug effects of renin-angiotensin

blockade such that improvement in endothelial function and reduction in oxidative stress and inflammation, rather than a lowering of blood pressure, account for the efficacy of these drugs in type 1 diabetic subjects. The data, when taken together for both types of diabetes, suggest that the greatest efficacy of ARBs and ACE-Is in decreasing DR is in reducing blood pressure in subjects in whom it is poorly controlled and in normotensive subjects in whom DR is absent or minimally present. These findings have led to the current American Heart Association guidelines of a target goal for blood pressure of <130/80 mmHg or below the 90th percentile for age, sex, and height, whichever is lower, for individuals with diabetes.

Fenofibrate, a peroxisome proliferator-activated receptor- $\alpha$  agonist, was shown in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study to reduce the incidence of laser treatment for CSME by 31% and for PDR by 30% in subjects with type 2 diabetes (18). In a smaller substudy in which retinopathy severity was determined by grading fundus photographs, fenofibrate treatment was associated with a decrease in the progression of retinopathy. To date, no definitive clinical trials have shown that lowering serum total or LDL cholesterol using statins reduces the incidence and progression of DR. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial may provide further insight regarding intensive control of lipids in reducing the incidence and progression of retinopathy in people with type 2 diabetes (19).

#### **Epidemiological evidence of changes in management practices of individuals with diabetes**

**Controlling blood glucose.** Changes in the monitoring and management of glycemia have resulted in the lowering of glycosylated hemoglobin over the past 30 years in some individuals with type 1 diabetes. For example, in subjects with type 1 diabetes in the WESDR, dramatic changes have occurred in how glycemic control is monitored (from testing urine to home blood glucose monitoring) and taking insulin three or more times per day (Table 2).

This has been associated with an absolute decrease of 3.5% in the mean glycosylated hemoglobin A1c (from 10.1% in 1980–1982 to 7.6% in 2005–2007) (Table 2). At the Steno Diabetes Center in Denmark, individuals diagnosed more recently with type 1 diabetes (1979–1984) were found to

TABLE 2

Changes in management and measurement of glycemia and blood pressure in subjects with type 1 diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 1980–2007

	Baseline 1980–1982	4 year 1984–1986	10 year 1990–1992	14 year 1994–1996	25 year 2005–2007
Urine dipstick testing for glucose (%)	71.8	41.6	13.5	7.9	N/A
Self blood glucose monitoring (%)*	N/A	72.3	80.2	85.8	90.7
Average number of blood glucose monitorings per day*	N/A	1.2	1.9	2.5	4.6
≥3 insulin injections per day or pump use (%)	3.6	11.5	24.3	38.3	84.5
Pump use (%)	1.0	1.4	1.4	3.4	35.5
Mean glycosylated hemoglobin A1c (%)	10.1	9.4	9.3	8.9	7.6
% controlled glycosylated hemoglobin A1c <7.0%	3.7	6.7	6.3	7.4	33.1
% taking ACE-Is or ARBs	N/A	0.9	10.9	19.9	56.8
Mean arterial BP (mmHg controlling for age)	100.2	94.7	93.3	92.9	92.2
% BP controlled <130/80 mmHg on antihypertensive medications	1.4	5.4	10.2	16.7	22.4
% of persons with ≥5 years of diabetes seen by an ophthalmologist within 1 year of study exam	56	54	67	74	67

\*Question not asked at baseline exam. BP, blood pressure; N/A, not applicable.

have lower mean glycosylated hemoglobin (8.4 vs. 8.9%) than those diagnosed in 1965–1969 (20).

Data from the WESDR and the Steno Diabetes Center are from predominantly white middle-class cohorts who are more likely to have access to care than uninsured or economically disadvantaged individuals. Preliminary data from the Chicago Childhood Diabetes Registry Family Study showed that in participants with type 1 diabetes seen between September 2004 and April 2009, the mean glycosylated hemoglobin A1c was 9.5%; 70% had a glycosylated hemoglobin A1c level of more than 8%; and only 62% were taking three or more insulin injections per day or using an insulin pump. These data suggest that similar improvements in glycemic control in economically disadvantaged individuals with type 1 diabetes as compared to middle class type 1 patients are not being achieved (R. Lipton, personal communication). Thus, caution must be taken in assuming that improvements in achieving intensive glycemic control reported in the Wisconsin and Danish studies are also occurring in those with limited access to care.

Data from the National Health and Nutrition Survey (NHANES) has shown that there have been changes by clinicians in the management of glycemia in people with type 2 diabetes after publication of the UKPDS results in 1997 (21–23). There was increased use of more than one oral hypoglycemic agent (metformin and thiazolidinedione in 1999–2004) from the predominant use of one type of oral agent (sulfonylureas in 1988–1994) (21,22). This was accompanied by a drop in the mean glycosylated hemoglobin A1c levels from 7.8 to 7.2%, attaining glycosylated hemoglobin levels of <7.0% in 41% and 58% of those with type 2 diabetes in the U.S. population examined in the NHANES in 1999–2000 and 2005–2006, respectively (24). This improvement in glycemic control among medication-treated individuals with type 2 diabetes was found in non-Hispanic whites but not in non-Hispanic blacks or Mexican Americans (21).

To our knowledge, there are no long-term longitudinal epidemiologic data showing similar changes in management and glycemic control in subjects with type 2 diabetes in developing countries, where the prevalence of type 2 diabetes is expected to increase by 2½ times by the year 2030.

**Controlling blood pressure.** Some long-term epidemiological studies have also shown changes in the management of hypertension and resulting changes in blood pressure over time. For example, in the Steno Diabetes Center study, the time from diagnosis of type 1 diabetes to initiation of antihypertensive treatment was shortened, the use of ACE-I became more frequent, and the mean arterial blood pressure decreased with each more recent period of diagnosis of type 1 diabetes (from 1965–1969 through 1979–1984) (20). In the WESDR, when using the current ADA guidelines of a target blood pressure of <130/80 mmHg for diabetic individuals with hypertension, the percentage of type 1 diabetic participants with blood pressure reaching this goal improved from 1.4% at the 1980–1982 examination to 22.4% at the 2005–2007 examination (Table 2). At the last examination, 56.8% of those with type 1 diabetes with hypertension were taking ACE-I or ARB.

Blood pressure control appears to be improving in subjects with type 2 diabetes. In the NHANES examination from 1999–2000 to 2005–2006, the frequency of controlled hypertension (<130/80 mmHg) increased from 16 to 29% (24).

**Changes in eye care.** In the WESDR, only 67% of subjects with Diabetic Retinopathy Study (DRS) high-risk characteristics for severe visual loss or CSME had been examined by an ophthalmologist within two years prior to the study examination. Lack of symptoms, not being told they needed such examinations, and the cost of the examinations were the main reasons given by the subjects for not being seen by an ophthalmologist. Guidelines for whom, when, and how often to be seen were developed based on these and other observations, which showed many diabetic subjects with a higher risk of vision loss were not receiving timely dilated eye examinations. Educating diabetic patients and their physicians about the need for timely eye examinations led the National Eye Institute to initiate the National Eye Health Education Program in the early 1990s. That program, along with the World Health Organization's Saint Vincent Declaration, led to the initiation of screening programs in the U.K. and other European countries for the timely detection and treatment of patients with PDR who have a higher risk of visual loss and CSME. In areas where active screening for DR has been implemented, lower incidence of severe VI has been found (25).

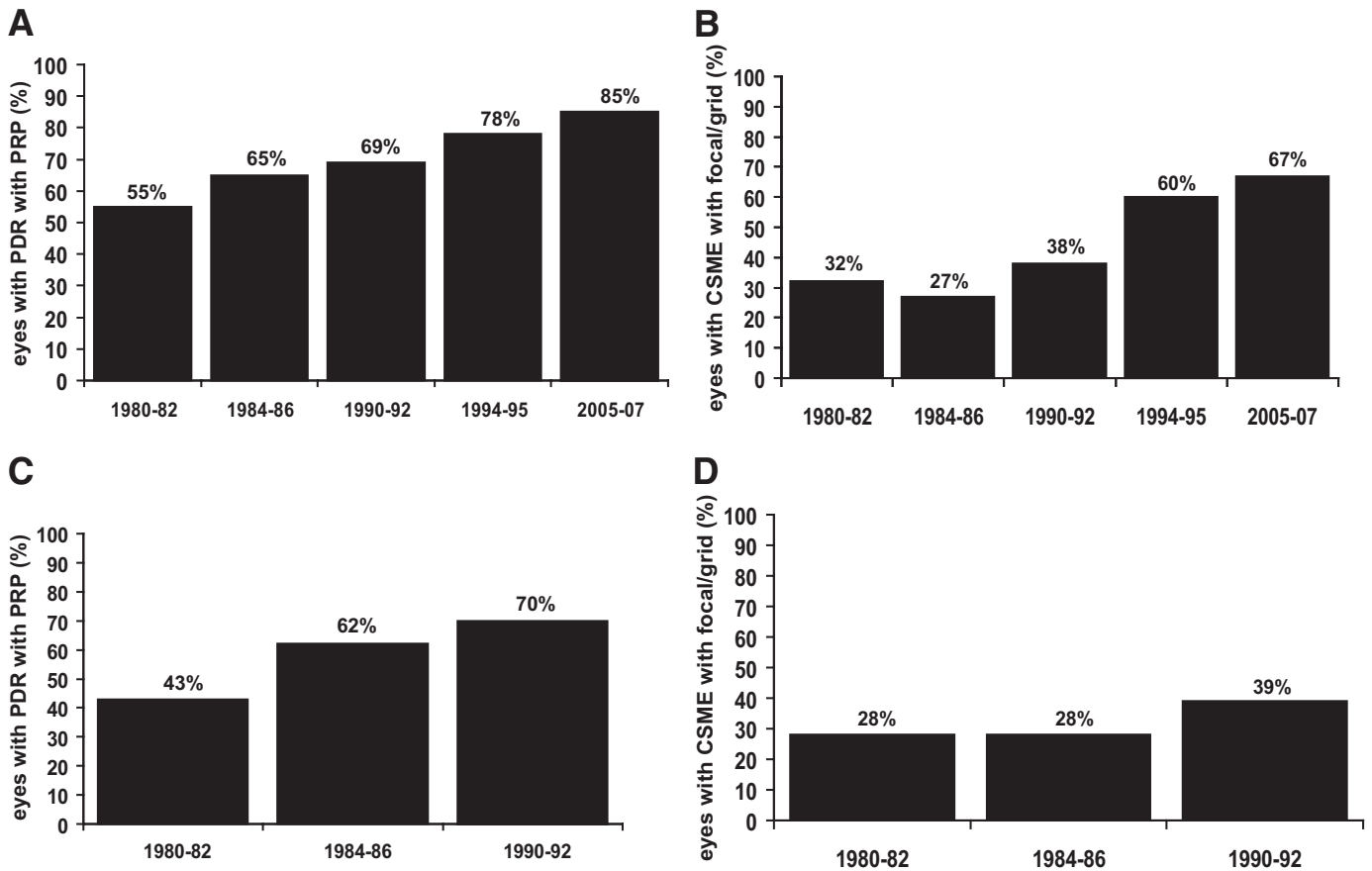


FIG. 1. Prevalence of right eyes with PDR treated with panretinal photocoagulation (PRP) (A) and CSME treated with focal and/or grid photocoagulation (B) in WESDR subjects with type 1 diabetes, and PDR treated with PRP (C) and CSME treated with focal and/or grid photocoagulation (D) in WESDR subjects with type 2 diabetes.

**Treatment with photocoagulation.** Two randomized controlled clinical trials, the DRS and the Early Treatment Diabetic Retinopathy Study (ETDRS), demonstrated the efficacy of photocoagulation in preventing visual loss in subjects with PDR and CSME, respectively (26,27). In the WESDR from 1980 through 1982, a high proportion of eyes with PDR and CSME in subjects with diabetes had not received panretinal photocoagulation or focal and/or grid photocoagulation treatment (Table 1) (28). Over time, there has been an increase in the proportion of eyes with PDR and CSME that have had panretinal and macular focal/grid treatment, respectively (Fig. 1).

**Epidemiological evidence of changes in incidence and prevalence of PDR, CSME, and VI.** In 1980–1982, PDR, CSME, and severe VI were frequent in subjects with 15 or more years of diabetes (Table 1). There is evidence that the prevalence and incidence of DR may be decreasing in subjects more recently diagnosed with type 1 diabetes. Hovind et al. (20) first showed a declining incidence of PDR and macular edema in a study of 600 patients with type 1 diabetes diagnosed between 1965 and 1984 in Denmark. The cumulative incidence of PDR and macular edema after 20 years of diabetes declined from 31 to 19% in those diagnosed from 1965 to 1969 to 13 and 7%, respectively, in those diagnosed from 1979 to 1984. There was also significant improvement in visual acuity and less severe VI prevalence in those diagnosed with type 1 diabetes more recently than those diagnosed in earlier periods. These changes were attributed to improved glycemic control, more aggressive treatment of blood pres-

sure sooner after diagnosis of diabetes, and reduced smoking rates in the more recently diagnosed type 1 diabetic group than in previous years.

The Linköping Diabetes Complications Study examined the incidence of laser-treated severe retinopathy (both PDR and CSME) after 20 years of diabetes in an unselected population with type 1 diabetes diagnosed from 1961 to 1984 (29,30). The authors reported a statistically significant decline in the cumulative proportion with severe laser-treated DR after 25 years of type 1 diabetes from 47% in subjects diagnosed in 1961–1965 to 24% in subjects diagnosed in 1971–1975. There was no significant decline in the cumulative proportion with NPDR in the same time period in this study. The Pittsburgh Epidemiology of Diabetic Complications Study did not show a significant decrease in PDR with more recent year of type 1 diabetes diagnosis over a 25-year period of follow-up (31).

In the WESDR, the annualized estimates for the progression of DR and the incidence of PDR, CSME, and VI were higher in the first 12 years of the study (1980–1992) than in the latest 13 years of the study (1994–2007) (Fig. 2) (32–35). There was also evidence in the WESDR of lower prevalence of PDR (4% lower per more recent period) and VI (9% lower per more recent period) but not of macular edema in those diagnosed with type 1 diabetes more recently than those diagnosed in the past (Figs. 3 and 4). The relationships remained when adjusting for hypertension and glycosylated hemoglobin levels over time. The WESDR findings are consistent with a decline in the prevalence of diabetic nephropathy and better survival in

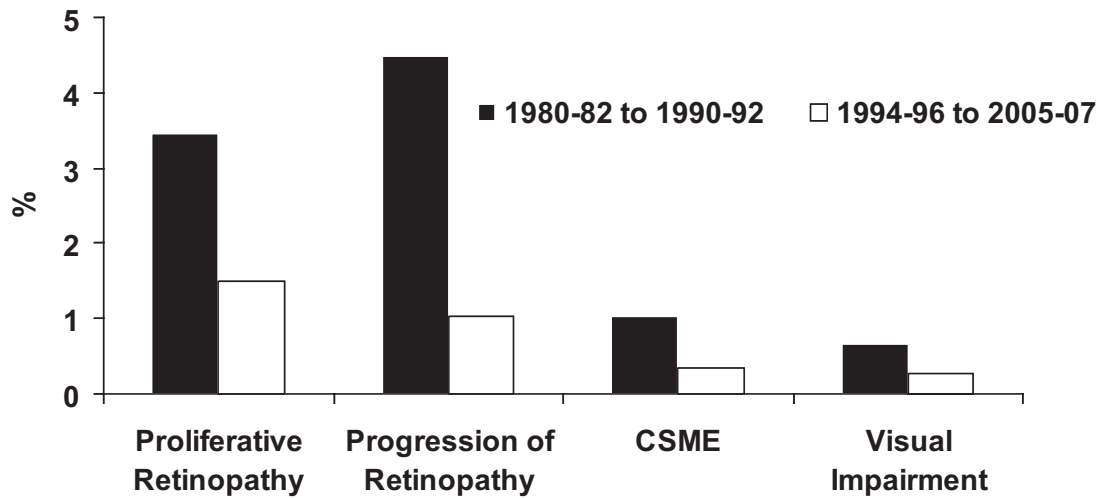


FIG. 2. Estimated annual incidence of PDR, progression of DR, incidence of CSME, and incidence of VI in type 1 diabetic subjects in two examination periods (1980–1992 and 1994–2007) in the WESDR.

people diagnosed with type 1 diabetes in more recent periods. In the Wisconsin Diabetes Registry Study (36), among an incipient cohort of individuals diagnosed with type 1 diabetes 7 to 12 years after the WESDR, the prevalence of PDR at 15 or 20 years of diabetes was significantly lower than in the WESDR.

It is possible that the estimates of a reduction in the incidence of DR and other complications associated with the improvement in glycemic control reported in the

WESDR and Hovind studies may actually underestimate the effect in those currently being diagnosed with type 1 diabetes (20,32–35). The DCCT findings showed that intensive therapy was more beneficial when started earlier in the course of type 1 diabetes, prior to the onset of DR. Four and ten years of additional follow-up of the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort after the study medication regimen was discontinued revealed that despite convergence of

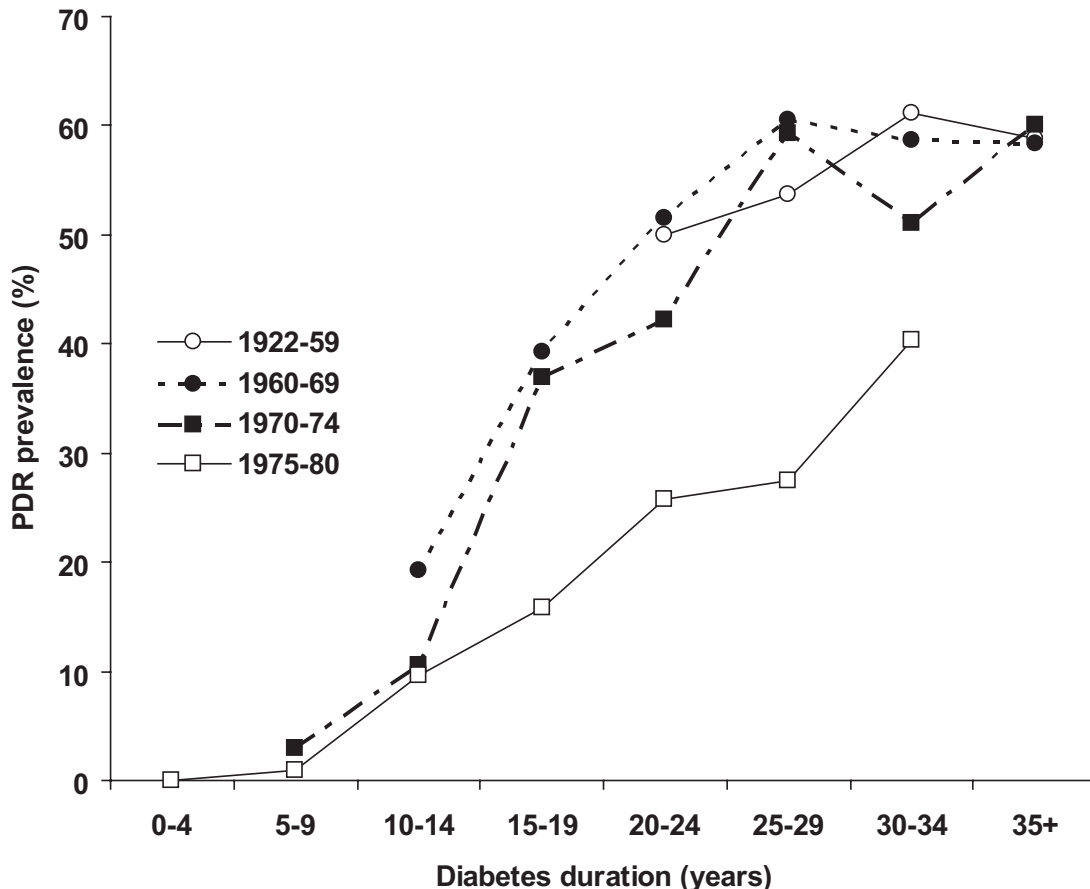


FIG. 3. Prevalence of PDR by diabetes duration and period of diagnosis (1922–1959, 1960–1969, 1970–1974, and 1975–1980) in the WESDR. Figure adapted from Klein et al. (32).

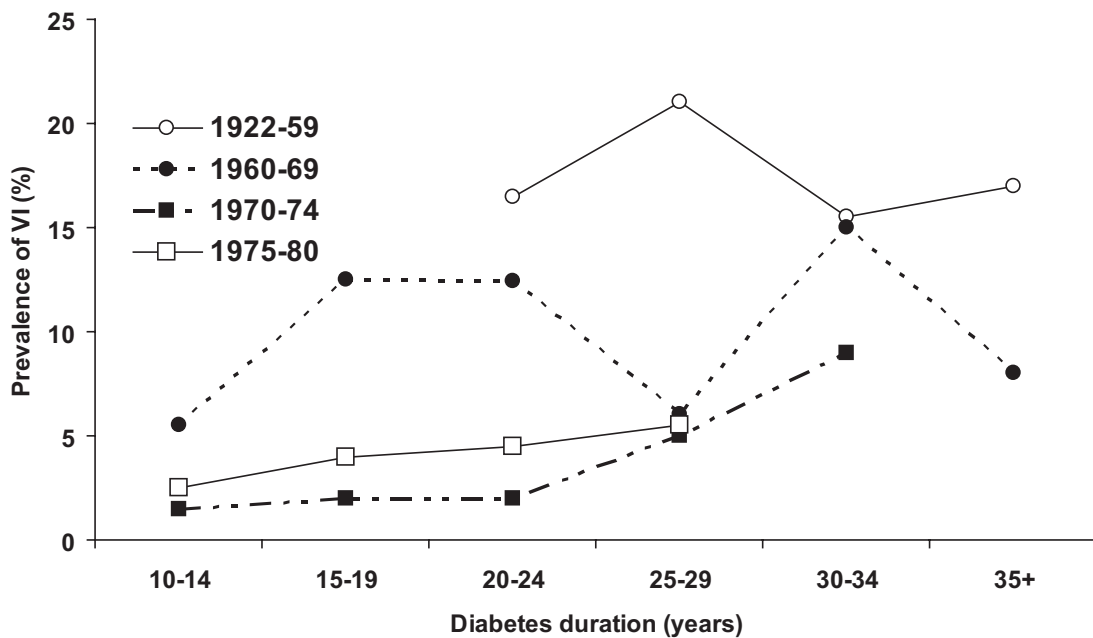


FIG. 4. Prevalence of VI (defined by best corrected visual acuity of 20/40 or worse in the better eye) by diabetes duration and period of diagnosis (1922–1959, 1960–1969, 1970–1974, and 1975–1980) in the WESDR.

glycosylated hemoglobin levels in the intensive and conventional groups, the protective effect of glycemic control was maintained in the intensive group, an effect labeled metabolic memory (11). A comparison of the conventional with the intensive DCCT/EDIC cohort and a population-based cohort showed that after 30 years of diabetes, the cumulative incidence of PDR was 50% in the DCCT conventional treatment group, 47% in the population-based cohort, and 21% in the DCCT intensive group (37). These data suggest that if intensive glycemic control can be achieved and maintained in subjects with newly diagnosed type 1 diabetes, a further decrease in the incidence of DR and visual loss is likely in the future.

There is, however, less certainty as to whether there has been a similar decline in the prevalence and incidence of DR in subjects with type 2 diabetes. In WESDR participants 40 years of age or older in 1980–1982 with type 2 diabetes, the crude prevalence of any DR and visually threatening DR was higher (50 vs. 35% and 10 vs. 3%, respectively) than in subjects with type 2 diabetes in the Beaver Dam Eye Study in 1988–1990, suggesting a significant drop in prevalence over the 8-year period between the two studies (38). On the other hand, in the Blue Mountains Eye Study in Australia, the prevalence of any DR increased from 27% in 1992–1994 to 34% in 1997–2000. This study found a lower prevalence of moderate to severe DR in those examined more recently (39). Similarly, the overall prevalence of DR in the Melbourne Visual Impairment Study increased slightly from 29% in 1992 to 36% in 1997 (40,41).

Medicare data from two cohorts (1994–1999 and 2000–2005) of individuals 65 years or older and newly diagnosed with type 2 diabetes were compared. There was a decrease in the cumulative incidence of DR, PDR, and macular edema of 17, 23, and 9%, respectively (42), in the more recently diagnosed cohort.

The duration-specific prevalence of NPDR was lower and PDR was similar in a study comparing members of an HMO with type 2 diabetes in 1997–1998 compared with the

WESDR cohort in 1980–1982 (43). The authors concluded that the lower prevalence of NPDR was due to earlier diagnosis of type 2 diabetes and more aggressive control of blood glucose (HbA1c 7.8% vs. 10.4%) and blood pressure (139/79 vs. 147/79 mmHg) in their clinic compared with the WESDR cohort. The lack of a difference in PDR was hypothesized to result from rapid intensification of glucose control in the HMO group. However, while rapid management of hyperglycemia in poorly controlled diabetic individuals may be responsible for the progression of DR in some diabetic individuals, previous clinical trials have not shown a difference in the incidence of PDR between intensive and conventional treatment arms of the studies. Ascertainment differences for DR between studies may also explain these findings (44).

To our knowledge, no recent U.S. national estimates of the prevalence of DR and visual acuity in subjects with type 2 diabetes have been released since the UKPDS results were published in 1997. Comparison of data from the 1988–1994 NHANES III with data from the 2005–2008 NHANES (not yet published) may provide useful information regarding changes in the frequency of these ocular complications in type 2 diabetic individuals. However, because of significant changes in diagnostic criteria for defining the presence of type 2 diabetes in the population and different methods of assessing the presence of retinopathy in type 2 diabetic individuals (digital vs. film, area of retina photographed), such comparisons may be limited. To our knowledge, no data on the ocular lesions of diabetes or their functional visual sequelae are available from developing countries, where the prevalence of diabetes is expected to increase as their populations become more sedentary and obese.

**New interventions.** While the incidence of late vision-threatening complications such as CSME and PDR has decreased considerably as a result of intensive glycemic and blood pressure control, and while the DRS and the ETDRS have shown the efficacy of timely intervention with photocoagulation for those who develop these complica-

tions, considerable numbers of diabetic individuals who suffer visual loss as a result of these complications still remain. Adjunct medical approaches have been developed—some of which were shown to have no efficacy in clinical trials (e.g., aldose reductase inhibitors), while others are still under evaluation (e.g., protein kinase C inhibitors, intravitreal triamcinolone) (45,46).

Among all these new interventions, a phase 3 controlled multicenter clinical trial of vascular endothelial growth factor (VEGF) inhibitors to reduce leakage and retinal thickness in eyes with macular edema was initiated (47). The trial was based on a finding that increased VEGF levels in the retina and vitreous of eyes with DR increases retinal vessel permeability by affecting phosphorylation of tight junction proteins. The trial showed that the anti-VEGF agent bevacizumab with prompt or deferred ( $\geq 24$  weeks) focal/grid laser reduced macular thickening and improved vision at both the one and two-year follow-ups. There were no systemic side effects, and mortality did not increase; however, there were three cases of injection-related endophthalmitis in the treated group. Further evaluation of the risks and benefits of anti-VEGF treatment is needed in large phase 3 long-term randomized controlled clinical trials.

**Future needs.** Data from the WESDR and other studies have shown associations of hyperglycemia with the incidence and progression of retinopathy and other microvascular and macrovascular complications in diabetic subjects (48). However, while intensive glycemic control is beneficial in reducing complications, it is associated with severe hypoglycemic reactions sometimes resulting in coma or seizures, making it difficult for many type 1 diabetic individuals to adhere to an intensive insulin treatment regimen (49). Thus, because intensive insulin treatment is associated with significant morbidity (e.g., hypoglycemia) and because glycemia is difficult to control, it is important to improve the technology to achieve more physiologic administration of insulin. It is also important to identify genetic and novel risk factors that can be used to develop new approaches to prevent the incidence and progression of DR.

Current population-based estimates of prevalence and incidence of DR and continuing surveillance are needed to estimate the burden of these complications as well as the effectiveness of new interventions, e.g., use of fenofibrate and intravitreal injections of anti-VEGF agents over time. This is especially important in a time of changing prevalence of complications and evolving preventive therapies. It is also important to understand how methodological (e.g., how the cohort was ascertained, effects of nonparticipation, inaccuracy of dating onset of type 2 diabetes, effects of censoring due to mortality) and biological issues (e.g., metabolic memory, rapid intensification of glycemic control) will affect estimates of incidence and progression of DR in future epidemiological studies.

**Summary.** Data from epidemiological studies have shown remarkable improvements in the care and management of diabetes associated with significant decreases in the prevalence and incidence of DR and VI in type 1 diabetic individuals over the past 30 years. Limited long-term epidemiological data are available to determine whether similar trends exist for individuals with type 2 diabetes. Epidemiological studies have disclosed the high incidence of DR and its association with poor glycemic and blood pressure control. They have also described the infrequency of dilated eye examinations and infrequent timely

treatment with photocoagulation in patients with late stages of DR. New technologies to monitor glycemic control and new drugs to treat hyperglycemia and hypertension have proven effective in decreasing vision-threatening retinopathy. These, coupled with the development of educational and surveillance programs for detection and early treatment of ocular complications, have played major roles in this decrease in DR and VI in subjects with type 1 diabetes and possibly in subjects with type 2 diabetes. While this represents a public health success for those with access to health care, it is unclear whether similar improvements in management are occurring in the growing number of people with type 2 diabetes in areas where access to health care is poor.

#### ACKNOWLEDGMENTS

This research is supported by National Institutes of Health Grants EY03083 and EY016379 (R.K. and B.E.K.K.) and, in part, by Research to Prevent Blindness (R.K. and B.E.K.K., Senior Scientific Investigator Awards), New York, New York.

R.K. has served as a consultant to AstraZeneca, Lilly, and Pfizer. No other potential conflicts of interest relevant to this article were reported.

R.K. wrote the manuscript and researched the data. B.E.K.K. reviewed and edited the manuscript and wrote parts of the manuscript.

The authors thank Scot Moss, Kristine E. Lee, and Chelsea Myers for contributing their statistical expertise, and Heidi Gutt for technical assistance and editing of the manuscript.

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