

Has the Frequency of Proliferative Diabetic Retinopathy Declined in the U.S.?

Randomized controlled clinical trials provide evidence that intense glucose and blood pressure control result in a reduction in the incidence and progression of retinopathy and visual loss in people with diabetes (1–4). In the Diabetes Control and Complications Trial (DCCT) (1), intensive insulin treatment was found to reduce the risk of retinopathy progression in people with type 1 diabetes by 76% in those without and 54% in those with retinopathy at baseline compared with conventional treatment. In the U.K. Prospective Diabetes Study (UKPDS) (2), after 12 years of follow-up of people newly diagnosed with type 2 diabetes, intensive glycemic control reduced the rate of progression of diabetic retinopathy by 21% and the need for laser photocoagulation by 29% compared with conventional treatment. In the UKPDS (3), tight blood pressure control in hypertensive patients independently resulted in a 34% reduction in the rate of progression of retinopathy, a 35% reduction in retinal photocoagulation, and a 47% reduction in the deterioration of visual acuity by three lines or more compared with conventional blood pressure control. The Appropriate Blood Pressure Control in Diabetes Trial (4) showed that intensive blood pressure control reduced the progression of diabetic retinopathy by 28% in normotensive subjects with type 2 diabetes.

Despite these findings, there are few population-based data demonstrating that application of intensive treatment of blood glucose and blood pressure has resulted in fewer micro- and macrovascular complications in diabetic patients (5,6). Data from one recent study in Denmark (5), in which individuals with type 1 diabetes were followed for ≥ 20 years, showed a large decrease in the cumulative incidence of diabetic microvascular complications, including proliferative retinopathy (12.5 vs. 31.2%) and macular edema (7.4 vs. 18.6%) in people with di-

abetes onset between 1979 and 1984 compared with people with diabetes onset between 1965 and 1969. This was attributed to improved glycemic control (HbA_{1c} 8.5 vs. 8.9%) and early aggressive antihypertensive treatment (mean arterial blood pressure 102 vs. 95 mmHg) in the more recently diagnosed group compared with the earlier diagnosed group, suggesting the efficacy of these treatments in the population. However, declines in the incidence of severe retinopathy have not been found in other populations (6).

Longitudinal population-based data comparing the current prevalence of complications with those in the past are lacking in individuals with type 2 diabetes. With this in mind, Brown et al. (7) sought to fill this gap by comparing data of people with type 2 diabetes who were currently (1997–1998) under care in the Kaiser Permanente Northwest health maintenance organization in the Portland area with data from type 2 diabetic patients participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR; 1980–1982) (7,8). Because of the lower mean HbA_{1c} levels (7.9 vs. 10.4%) and mean systolic blood pressure levels (139 vs. 147 mmHg) in the Kaiser Permanente Northwest compared with the WESDR cohort, they anticipated lower rates of both nonproliferative and proliferative diabetic retinopathy in the Kaiser Permanente Northwest compared with the WESDR cohort. They did find lower prevalence of nonproliferative diabetic retinopathy but comparable proportions of proliferative diabetic retinopathy. Brown et al. attribute these findings, in part, to a possible deleterious effect of improved glycemic control. However, it may be that improved treatment of blood pressure, serum lipids, and renal disease has led to improved survival in those with type 2 diabetes. This prolongation of life leads to longer duration of diabetes, which is still likely to have increased the risk of proliferative diabetic retinopathy.

It is also true that there is a strong possibility of detection bias in the Kaiser Permanente Northwest cohort, as people with early diabetes and no or minimal retinopathy are less likely to be referred to retinal specialists for care than those with a longer duration of diabetes or those with visual symptoms. Furthermore, 16% of the study-eligible Kaiser Permanente Northwest patients with shorter duration and less severe disease did not receive a retinal examination that, if included, would likely have resulted in a lower prevalence of proliferative diabetic retinopathy. Other study differences in the approaches used to detect and define the presence and severity of diabetic retinopathy between Kaiser Permanente Northwest and WESDR are also likely to have resulted in differences found between the two groups.

The possibility that the similarity of the prevalence of proliferative diabetic retinopathy between the Kaiser Permanente Northwest and the WESDR cohorts may be real and due to “accelerated progression of proliferative retinopathy after the rapid intensification of glucose control,” as suggested by Brown et al., deserves further attention. Initial worsening of retinopathy had been reported in feasibility clinical trials of intensive treatment in patients with type 1 diabetes (9–11). In the DCCT, early worsening of retinopathy in the first year of treatment of the intensive therapy group in the secondary-intervention cohort was observed (12). However, after 3 years the beneficial effect of intensive insulin treatment had increased. Accelerated progression has been reported in people with type 2 diabetes (13,14). In the first 12 months of the VA Cooperative Study on glycemic control and complications in type 2 diabetes (15), there was a statistically insignificant trend toward a higher proportion of worsening of retinopathy in patients with nonproliferative diabetic retinopathy at baseline in the intensive versus the conventional

treatment. However, the incidence of proliferative diabetic retinopathy was similar in both intensive and conventional treatment arms of that study. Accelerated progression was not described in the UKPDS (2). While it is possible that accelerated progression may account, in part, for some of the proliferative diabetic retinopathy seen in the Kaiser Permanente Northwest, it is more likely that more intense treatment with insulin in type 2 diabetic subjects is a response to disease that is progressing due to poorer glycemic control. People whose eyes have severe retinal ischemia and progressing retinopathy are usually in need of better glycemic control (initiated sometimes by physicians with the rationale that the development and progression of complications justify more aggressive treatment). While it is unlikely that accelerated progression is the underlying reason for differences in prevalence of proliferative diabetic retinopathy between the WESDR and Portland groups, further research is needed to evaluate this possibility.

In summary, the use of historical controls to assess change in retinopathy frequency is an inadequate approach for monitoring the frequency and severity of diabetic retinopathy and other chronic complications of diabetes and the response to changing treatments. However, the findings of Brown et al. show that despite improvement in levels of glycemia and blood pressure, proliferative diabetic retinopathy remains prevalent. This can be interpreted to support the need for regular ophthalmologic examinations through a dilated pupil of people with type 2 diabetes. Early detection and treatment with photocoagulation is beneficial in preventing visual loss from this complication (16).

RONALD KLEIN, MD, MPH

From the Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison, Wisconsin.

Address correspondence to Ronald Klein, MD,

MPH, Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, 610 North Walnut St., 405 WARF, Madison, WI 53726-2336. E-mail: kleinr@epi.ophth.wisc.edu.

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