Diabetic Retinopathy

Contemporary prevalence in a well-controlled population

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OBJECTIVE — To measure the extent to which modern intensified risk factor control has lessened the duration-specific prevalence of diabetic retinopathy and, therefore, has decreased the risk of blindness in Americans with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Intensified control of blood glucose and blood pressure has prevented diabetic retinopathy in randomized controlled trials. There is as yet no confirmation that subsequent treatment intensification in the community has had the same result. We identified all 6,993 members of a health maintenance organization, Kaiser Permanente Northwest (KPNW), who, in 1997–1998, had dilated retinal examinations and verifiable data of diagnosis of type 2 diabetes. We plotted prevalence by time since diagnosis for background diabetic retinopathy (BDR) and proliferative diabetic retinopathy (PDR) and compared these results to identically derived 1980–1982 results from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). We estimated multivariate predictive models.

RESULTS — Mean (± SD) HbA_{1c} in KPNW was 7.84 ± 1.26% versus 10.37% (standardized) in the WESDR. KPNW blood pressure averaged 138.6 ± 13.8/79.5 ± 7.4 mmHg compared with 147.0/79.0 in the WESDR. BDR was much less prevalent in KPNW, but PDR prevalence appeared unchanged. BDR preceded diagnosis in 20.8% of the WESDR subjects but only 2.0% of KPNW subjects. However, in both populations, the first cases of PDR appeared similarly, soon after diagnosis.

CONCLUSIONS — Earlier diagnosis and more aggressive control of blood glucose and blood pressure decreased the duration-adjusted prevalence of *background*, but not of sight-threatening *proliferative* retinopathy. More population-based research is needed to replicate and explain this unexpected finding. Detecting and treating PDR should not be neglected on the assumption that risk-factor control has minimized its prevalence.

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Diabetic retinopathy is the third most common cause of blindness in the U.S. and the leading cause of new blindness in individuals 20–74 years of age (1). Retinopathy threatens sight once proliferative diabetic retinopathy (PDR) or macular edema (ME) appears (2). Among individuals at high risk in the 1960s through 1980s, randomized trials showed that annual examination plus laser photocoagulation could halve the incidence of blindness (3,4). Computer modeling subsequently showed that periodic screening was cost-effective (5,6). Annual or biennial screening is now a standard of care (7,8).

In the 1990s, randomized trials confirmed that control of hyperglycemia and hypertension could prevent retinopathy (9–13). These findings accelerated a movement toward intensified risk-factor control (14). The resulting improvements, however, fueled speculation that annual retinal screening was no longer justified in many patients (15,16). Quality measurement organizations lengthened the screening interval for non–insulin-using patients with relatively good HbA_{1c} levels.

To assess the contemporary threat from retinopathy, we compared the contemporary prevalence of background diabetic retinopathy (BDR) and PDR to the prevalence in a historical population—participants in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). WESDR measured baseline diabetic retinopathy in 1980–1982, before aggressive risk-factor control was widespread (17).

RESEARCH DESIGN AND METHODS

Research setting and study population

The subjects of this study were members of a long-established nonprofit group-model health maintenance organization called Kaiser Permanente Northwest (KPNW) and had type 2 diabetes. The methods used to create the KPNW Diabetes Registry are described elsewhere (14). Validation studies have shown the registry to be over 99% sensitive and 99% specific for diagnosed diabetes (14).

Inclusion criteria for the present study were *1*) type 2 diabetes, *2*) known date of diagnosis, *3*) 2 full years of health plan eligibility in 1997 and 1998, and *4*) at least one KPNW dilated retinal examination between 1 January 1997 and 31 December 1998. Diagnosis date was not calculated unless registrants had a full

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Abbreviations: ADR, accelerated diabetic retinopathy; BDR, background diabetic retinopathy; DCCT, Diabetes Control and Complications Trial; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; KPNW, Kaiser Permanente Northwest; ME, macular edema; PDR, proliferative diabetic retinopathy; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

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

See accompanying editorial, p. 2691.

year of health plan membership without any indication of diabetes before entering the registry. Case subjects who were diagnosed before 1988, when only inpatient data were available, also were excluded. Subjects with type 1 diabetes were excluded to allow comparison with the older-onset WESDR cohort (18). We also excluded individuals known to be blind (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 369.4).

Ascertainment of retinal status

We identified retinal status from inpatient discharge diagnoses but primarily from encounter and problem-list diagnoses in KPNW's comprehensive electronic medical record, which began in 1995 and 1996. To ascertain BDR, PDR, and ME, we considered a range of potential ICD-9-CM codes and, to validate local coding practices, compared code-specific prevalences in the study population to prevalences in an age- and sex-matched population of KPNW members without diabetes. We also checked coding against an independent study that compared KPNW outpatient diagnostic coding in 1999 to detailed descriptions in 500 individual medical records.

We ultimately defined PDR as the occurrence of ICD-9-CM codes 362.02 (PDR) or 379.23 (vitreous hemorrhage). These codes had high positive and negative predictive value for PDR in the 1999 validation study. To avoid overdiagnosing PDR, we ignored other codes that KPNW clinicians sometimes used for this condition. We defined background (nonproliferative) diabetic retinopathy by ICD-9-CM codes 362.01 (BDR), 250.5 (diabetes with ophthalmic manifestations), or 362.10 (background retinopathy unspecified). The latter code identified some cases of nondiabetic retinopathy (based on comparison with nondiabetic control subjects). For this and other reasons, we believe our coding somewhat overestimated BDR prevalence. We identified ME by the code 362.83 (retinal edema). This code proved to be very specific for ME but excluded a number of subjects whose ME was coded as BDR with a free-text annotation of ME.

Measurement of predictor variables

KPNW's HbA_{1c} results were based on the Diamat high-performance liquid chromatography method, the standard method used in the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study. We calculated long-term average HbA_{1c} (glycemic burden) and long-term mean lipid levels as the average of all values recorded from 1993 through 1998. We calculated mean blood pressure as the average of all blood pressure measurements recorded during 1997 and 1998. Individuals were considered to have had hypertension and insulin therapy if, at any time between 1987 and 1998, inclusive, they purchased an antihypertensive medication or insulin from KPNW. We calculated duration of therapy as the number of years between an individual's first and last purchases, using pharmacy data that extended back through 1987.

Analytic methods

To compare the duration-specific prevalence of diabetic retinopathy in 1997–1998 in KPNW to the duration-adjusted prevalence in 1980–1981 in southern Wisconsin, we plotted retinal status by duration of diabetes, just as the WESDR investigators did in two publications (18,19). These graphs do not show true cumulative incidence because they exclude retinopathy that may have occurred in individuals who died before the observation windows. Therefore, incidence is increasingly underestimated as duration increases.

The WESDR results were estimated from Fig. 2 of the third WESDR report (18), which displays data separately for insulin-using and non–insulin-using WESDR cohorts. The WESDR methods have been detailed elsewhere (17–21). Briefly, WESDR recruited subjects from lists of patients with diabetes created by 452 of the 457 primary care physicians practicing in southern Wisconsin in 1979. The investigators identified all patients who had been diagnosed after age 30 years and then excluded 34.5%, usually because of the absence of two confirmatory glucose tests. Random probability sampling was then applied within six strata defined by current use of insulin (yes or no) and tertiles of time since diagnosis, with fourfold oversampling in strata with disease durations >15 years. Of the recruitment sample, 76% completed the baseline examination (n = 1,370), which included seven-field fundus photography. Photographs were graded centrally by trained, blinded reviewers.

We estimated trend lines from annual mean prevalences using the Trend function in Microsoft Excel. To identify correlates of retinal disease progression, we estimated multivariate logistic models on all cases with fully complete data. We converted WESDR glycated hemoglobin values to the DCCT standard by the formula DCCT = 0.003 + 0.935 × WESDR (21).

RESULTS — We identified 11,985 individuals with type 2 diabetes who were members of KPNW throughout all of 1997 and 1998. Of these, 8,368 (70%) had a known post-1987 date of diabetes diagnosis. A total of 6,999 (84% of the 8,368) had retinal examinations during 1997 and 1998. Of these, six were found to be blind and were excluded, leaving 6,993 subjects.

Characteristics of the study sample are displayed in Table 1, together with baseline characteristics of the older-onset WESDR comparison sample, when known. Average age (± SD) was 61.9 ± 11.8 years (compared with 66.6 years in the WESDR), and 51% were male. Average age at diagnosis was 58.8 ± 11.8 years (vs. 54.8 years in the WESDR). Average duration of disease was 2.8 ± 2.6 years, much less than the 11.9 years reported by the WESDR. During the 6 years ending 31 December 1998, 98.5% had had at least one HbA_{1c} measurement and a large majority had multiple tests in each membership year. Mean HbA_{1c} was 7.84 ± 1.26% vs. 10.37% in the WESDR.

Total cholesterol results were available for 6,547 subjects (93.6%). The average mean total cholesterol was 220.3 ± 42 mg/dl (5.68 ± 1.08 mmol/l). During 1997 and 1998, patients averaged more than 10 medical care visits per year at which a blood pressure measurement was taken. All but 18 subjects had at least one blood pressure recorded. Systolic and diastolic blood pressures averaged 138.6 ± 13.8 and 79.5 ± 7.4 mmHg, respectively, compared with 147.0 and 79.0 mmHg in the WESDR.

Of the study population, 76% (5,105 of 6,993) purchased an antihypertensive medication during the 11-year study period, with a mean duration of use of 5.86 ± 4.0 years. Sixteen percent of the study sample used insulin. For these 1,119 individuals, the mean number of

Table 1—*Population characteristics: KPNW type 2 diabetes (1997–1998) and combined WESDR older cohorts (1980–1982)*

	KPNW					
	n	Mean	SD	Minimum	Maximum	WESDR
Mean total cholesterol	6,547	220.3	42.0	64	757	NA
Mean systolic blood pressure	6,975	138.6	13.8	92	211	147.02
Mean diastolic blood pressure	6,975	79.5	7.4	50	110	79.02
Mean HbA_{1c}	6,888	7.84	1.26	4.60	18.38	10.37
Proportion on antihypertensive therapy	6,993	0.76	—	—	—	NA
Duration (years) of hypertension therapy (if ever taken antihypertensives)	5,105	5.86	4.00	0	11	NA
Proportion on insulin therapy	6,993	0.16	—	—	—	0.49
Duration (years) of insulin therapy (if ever taken insulin)	1,119	2.8	2.5	0	8	NA
Age at diagnosis	6,993	58.8	11.8	13	95	54.77
Duration of diabetes	6,993	2.8	2.6	0	9	11.85
Age	6,993	61.9	11.8	17	96	66.62

The KPNW and WESDR groups differ in significant respects (see the text for details). NA, not applicable.

years on insulin was 2.8 ± 2.5. By sampling design, insulin use in the combined WESDR cohort was much higher (49%).

Ascertainment bias

The 16% of the study-eligible KPNW population who did not receive a retinal examination at KPNW during the study window were not statistically significantly different with respect to sex (males 53.0%, $P = 0.42$) or glycemic control (HbA_{1c} 7.93 vs. 7.84%, $P = 0.06$), but they were younger (58.6 vs. 61.9 years, $P < 0.0001$) and more recently diagnosed (duration 2.5 vs. 2.8 years, $P = 0.001$). In addition, they were less likely to be using insulin (12.7 vs. 16.1%, $P < 0.0001$), had lower systolic blood pressure (137.6 vs. 138.6 mmHg, $P = 0.022$), and had higher diastolic pressure (80.2 vs. 79.5 mmHg, $P = 0.0001$).

Table 2—*Rates of BDR, PDR, and ME by years since diabetes diagnosis*

Duration (years)	*n*	BDR	PDR	ME
1	2,015	2.63	0.74	0.45
2	879	5.46	0.80	0.46
3	823	6.08	1.22	0.61
4	757	8.32	1.06	0.40
5	650	10.77	1.85	0.46
6	536	13.25	1.31	0.93
7	517	17.41	2.90	1.16
8	419	22.20	2.15	2.86
9	396	22.73	5.05	1.52

Duration-specific prevalence

Table 2 details the prevalence of retinal disease by diabetes duration in the KPNW population. Prevalence increased with disease duration, with BDR more prevalent than PDR and PDR more prevalent than ME. (The bulge in year 1 is due to backlog additions to the registry in 1996 made possible by newly available electronic medical record data, i.e., individuals not yet using antihyperglycemic drugs or supplies.) Figure 1 plots these data for BDR and PDR against duration-specific prevalence for the insulin-using and non–insulin-using older-onset WESDR cohorts in 1980–1981. For PDR (Fig. 1*A*), duration-specific KPNW prevalence approximates the prevalences for the non–insulin-using WESDR group. For BDR, however, KPNW prevalence is much less than in either WESDR cohort. The best-fitting trend lines for PDR were linear and, for the WESDR BDR data, quadratic.

Correlates of retinal disease

Table 3 shows the results of three multivariate logistic models that regressed the occurrence of BDR, PDR, and ME on medical history variables. Of the 10 factors, 7 included in the BDR model returned statistically significant adjusted odds ratios (ORs). The OR for hypertension treatment was 1.69; for each 1-ml increase in mean systolic pressure, 1.02; and for hypertension treatment duration, 0.96. A 1 percentage point increase in mean long-term HbA_{1c} was associated with an OR of 1.44. Insulin use was associated with an OR of 1.52 and each year of insulin use with an OR of 1.09. The OR associated with a year of diabetes duration was 1.23. Age, sex, and mean total cholesterol had small, not statistically significant associations.

In a second analysis of 6,391 subjects for the presence of PDR (versus either no retinopathy or BDR), the odds associated with insulin therapy became nonsignificant, whereas the duration of insulin therapy remained significant at 1.15. The odds associated with a unit change in HbA_{1c} dropped somewhat to 1.33. Odds for diabetes duration, mean systolic blood pressure, and hypertension treatment duration became nonsignificant. The OR for hypertension treatment increased to 2.02.

In the multivariate model for ME (versus no ME), mean systolic pressure (OR 1.03/mmHg) and diabetes duration (OR 1.14/year) were significant predictors. However, the strongest correlate of ME by far was coexistent PDR (OR 26.63). ORs changed little when we removed PDR from the model.

CONCLUSIONS — We set out to measure the extent to which modern intensified medical practices have slowed the progression of diabetic retinal disease, as randomized clinical trials (9–13) would predict. We compared results from an earlier foundational study of diabetic retinopathy, the WESDR, to contemporary data from a population that had an extended history of improved glucose and

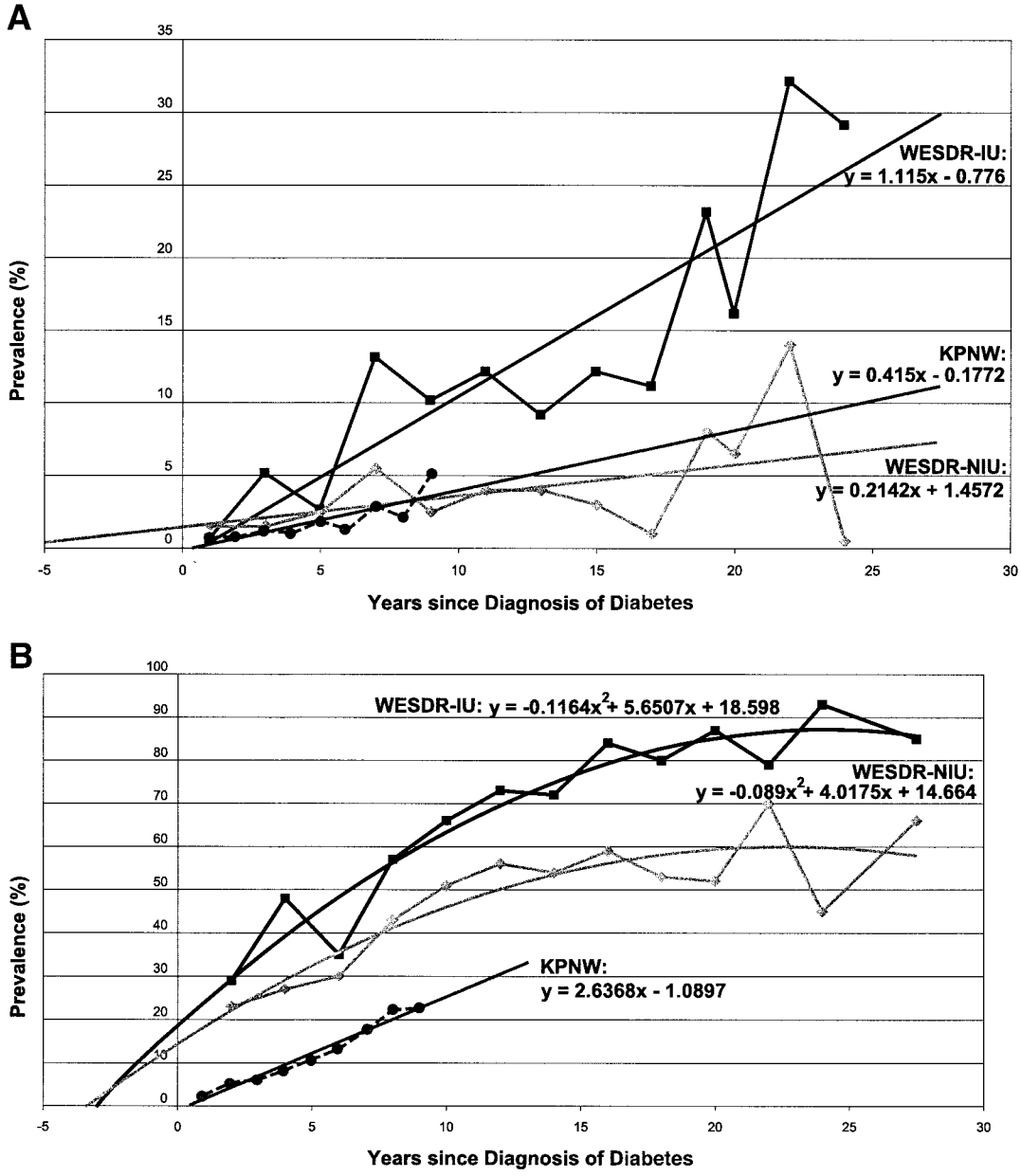

Figure 1—A*: PDR;* B*: BDR. Smooth lines are calculated trend lines and jagged lines connect data summarized by years since diagnosis. Black, square data points and lines are from the older insulin-using WESDR population (WESDR-IU). Light gray diamonds and lines represent data from the older non–insulin-using WESDR population (WESDR-NIU). Medium gray circles and lines represent data from the KPNW population with type 2 diabetes (KPNW). The lines connecting annual data from the KPNW population are dashed. Equations describe their adjacent trend lines.*

blood pressure control. We found a much lower duration-specific prevalence of BDR in the more recent data but a surprisingly unchanged prevalence of PDR. This finding suggests that the risk of blindness from PDR is not appreciably lower in modern patients despite dramatic improvements in mean risk-factor control.

We cannot rule out the possibility that less precise visualization and coding by KPNW clinicians affected our results. As previously described, we designed our ICD-CM-9 coding scheme conservatively to underestimate the prevalence of PDR and overestimate the prevalence of BDR. An independent review of 500 medical records for the year 1999 confirmed high positive and negative predictive values for our PDR assignment rules. Nevertheless, cases of advanced BDR may have been upcoded to PDR, and cases of early BDR may have been missed.

Similarly, lack of data on the 13% of the Kaiser Permanente population without a known date of diagnosis and on the 15% of the remainder without retinal examinations could have biased our PDR prevalence estimates upward if omitted cases had had less severe retinopathy. Diabetes diagnosis date could not be determined for individuals who joined the health plan with diabetes already diagnosed or who were diagnosed before

Table 3—*Results of multiple logistic regressions of retinal status on risk factors*

	BDR vs. retinopathy	PDR vs. BDR or none	ME vs. no ME
n	6,344	6,391	6,423
Predictor			
Age	1.00 (0.99–1.00)	**1.03 (1.01–1.06)**	0.99 (0.97–1.02)
Female	1.07 (0.88–11.38)	0.73 (0.46–1.14)	1.03 (0.56–1.92)
Duration	**1.23 (1.18–1.28)**	1.06 (0.97–1.16)	**1.14 (1.01–1.30)**
Mean HbA_{1c}	**1.44 (1.34–1.56)**	**1.33 (1.12–1.57)**	1.03 (0.80–1.33)
Hypertension treatment	**1.69 (1.28–2.25)**	**2.02 (2.02–4.00)**	2.25 (0.84–6.05)
Hypertension duration	**0.96 (0.93–0.99)**	0.96 (0.91–1.02)	0.93 (0.86–1.02)
Mean systolic blood pressure	**1.02 (1.01–1.03)**	1.02 (0.99–1.03)	**1.03 (1.01–1.05)**
Mean total cholesterol	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.01)
Insulin therapy	**1.52 (1.12–2.05)**	1.58 (0.81–3.08)	2.19 (0.90–5.34)
Duration of insulin therapy	**1.09 (1.02–1.16)**	**1.15 (1.02–1.30)**	1.03 (0.87–1.22)
PDR			**26.63 (13.24–53.59)**
Percent of variability explained*	12.9	9.2	24.1

Data are ORs (95% CI) unless otherwise indicated. *ORs in bold are statistically significantly different from 1.0 at $P \leq 0.05$. Based on the "pseudo R^2" entropy statistic, defined as $[a - b/a]$, where a is the -2 log likelihood of a logistic regression model with only the intercept term included, and b is the -2 log likelihood of the model when the intercept and all covariates are included. See ref. 41.

1988. The causes of missing examination dates included use of non–Kaiser-Permanente eye specialists, language and cultural barriers, forgetfulness, disorganization, and other causes of nonadherence to medical advice. (Most patients who were late for examinations received postcards and ultimately telephone reminders.)

Both study groups were population-based, WESDR by design, and KPNW by virtue of its large and representative (22) market share and remarkably stable membership (14), but probably differed in many respects beyond their hugely different glucose and blood pressure levels. Improved survival is one possible explanation of increased PDR in the KPNW population. Substantial improvement in age- and sex-adjusted mortality has been documented for the KPNW registry (14). Computer simulation models of diabetes (23–25) indicate that improved survival increases the prevalence of retinal disease by increasing the time available for its occurrence. However, simulation generally predicts increases in *both* background and proliferative disease. Our analysis revealed an apparent decrease in BDR.

The KPNW decrease in duration-specific BDR is partly attributable to earlier diagnosis of diabetes. Backward extrapolation of the cumulative prevalence function for BDR provides an indirect measure of the average delay between diabetes onset and diagnosis (26). The *x*-intercepts for BDR in Fig. 1*B* indicate that, relative to diagnosis, diabetes onset occurred ~4 years earlier in WESDR than in KPNW. If the *x*-intercept of the KPNW curve in Fig. 1*B* were shifted left 4 years, BDR prevalence in KPNW would approach (but not equal) the prevalence observed in the non–insulin-using WESDR cohort.

An intriguing aspect of the KPNW-WESDR comparison is that PDR prevalence does not follow BDR in shifting to the right in response to earlier diagnosis. Other researchers also have observed that time to PDR is independent of time to BDR (27). Our data raise the possibility that something occurring as a result of diagnosis helps trigger PDR. If so, a mechanism worth considering is accelerated diabetic retinopathy (ADR). Since the early 1980s, 13 studies have documented accelerated progression of PDR after the rapid intensification of glucose control (28–41). ADR has been observed in both type 1 and type 2 diabetic patients and has led to both transient and permanent progression, up to and including blindness. Further research is necessary to evaluate this hypothesis (42). An alternative explanation is that the U.K. Prospective Diabetes Study results have been misinterpreted (43), and intensified blood pressure and glycemic control actually do not prevent PDR in type 2 disease.

We conclude that earlier diagnosis of type 2 diabetes and more aggressive control of blood glucose and blood pressure have probably greatly decreased the duration-specific prevalence of *background* diabetic retinopathy since the WESDR, in settings where these actions have occurred. However, the duration-specific prevalence of sight-threatening *proliferative* retinopathy remains elevated. These findings should be confirmed by studies using expertly graded fundus photographs and in cohorts with longer follow-up. The possible role of ADR should be tested. In the meantime, detecting and treating PDR should not be neglected or de-emphasized.

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