Assessing Progress in Retinopathy Outcomes in Type 1 Diabetes

Comparing findings from the Wisconsin Diabetes Registry Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy

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OBJECTIVE—The Wisconsin Diabetes Registry Study (WDRS) cohort consisted of patients diagnosed with type 1 diabetes in the same geographic region as, but 8–34 years later than, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) cohort, providing a unique opportunity to assess changes in complications. We estimated the current prevalence and severity of diabetic retinopathy at 20 years of diabetes duration, compared these between eras, and evaluated the influence of diabetes management.

RESEARCH DESIGN AND METHODS—Twenty-year examinations, including fundus photographs, were completed on 305 WDRS subjects during 2007–2011. A subgroup of the WESDR cohort participated in one of four study visits during 1980–1996, at similar diabetes duration ($n = 583$). Adjusted ordinal logistic regression with three retinopathy severity categories was used to estimate odds ratios (ORs) of more severe retinopathy with diagnosis during an earlier era.

RESULTS—Mean hemoglobin A_{1c} (HbA_{1c}) was lower in WDRS than in WESDR (8.0% vs. 9.3% [$P < 0.001$], and 93.4% vs. 21.3% [$P < 0.001$]) used ≥3 daily insulin injections or an insulin pump. In WDRS, 18% had vision-threatening levels of retinopathy vs. 43% in WESDR. The adjusted OR of more severe retinopathy in the earlier era (OR 3.0 [95% CI 2.2–4.0]) was reduced by including 20-year HbA_{1c} in the model (OR 2.2 [1.6–3.0]).

CONCLUSIONS—Retinopathy severity at a diabetes duration of 20 years is lower in the more recent era of type 1 diabetes. Updated projections should be used when informing newly diagnosed individuals of prognosis and for health care cost assessments. Current glycemic control explained a limited amount of the difference.

T he burden of type 1 diabetes mellitus is high. Because type 1 diabetes onset is typically in childhood and adolescence, the effort to manage the disease and its sequelae lasts a lifetime. The majority of the morbidity and mortality associated with type 1 diabetes comes from chronic microvascular and macrovascular complications (1,2), including diabetic retinopathy (DR), a leading cause of preventable blindness in adults (3). Previously, some evidence of DR was present in most individuals by 15–20 years of diabetes duration (4,5). Recent reports, however, suggest less or less severe DR in the current era of diabetes care, not only at early durations (6,7) but perhaps even in long-standing type 1 diabetes (8–11). Studies report a decline in the incidence of severe DR across those diagnosed during the 1960s, 1970s, and early 1980s (8–10), but they may still overestimate the current level of retinopathy at 20 years of the disease (12).

"Glycemic memory" (13) implies that individuals practicing intensive diabetes management starting at early diabetes duration may have much lower rates or lesser severity of retinopathy today. Antihypertensive and lipid-lowering therapies now implemented earlier in the course of the disease could also impact the current level of retinopathy (8,14). The current course of retinopathy clearly has implications for individuals with type 1 diabetes as well as the health care system (15). Contemporary estimates on DR, DR severity, and diabetes self-management practices from population-based studies of individuals with type 1 diabetes in the U.S. are needed (12,15).

Differences in methods of identifying DR complicate the evaluation of time trends in retinopathy (16,17). In our two studies, protocols for data collection included the same gold standard methods for objectively measuring retinopathy. The Wisconsin Diabetes Registry Study (WDRS) has followed a population-based cohort of individuals comprehensively since diagnosis of type 1 diabetes (6,18). This cohort was enrolled from a geographically defined region overlapping the study area of the landmark and also population-based Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (4). We sought to capitalize on the unique opportunity presented by these two cohorts to investigate change in the course of DR. Specifically, we aimed to do the following: *1*) provide contemporary estimates of the prevalence and severity of DR and diabetes self-management in the population after type 1 diabetes duration of 20 years, *2*) compare retinopathy severity between time periods, and *3*) evaluate whether changes in glycemic control and related diabetes management factors explained the differences seen in retinopathy between these time periods.

RESEARCH DESIGN AND METHODS

The WDRS population
The WDRS is an incident population-based cohort study of type 1 diabetes

complications and their risk factors, from diagnosis through a duration of 20 years (6,18–21). During May 1987 through April 1992, all residents ≤30 years of age in 28 counties of central and southern Wisconsin newly diagnosed with type 1 diabetes (by classic diabetes symptoms and requirement for exogenous insulin, according to World Health Organization criteria at the time [22]) were eligible. Patients were referred by physicians, nurses, diabetes educators, family members, or self-report. Hospitals and clinics were called every 3 months to ascertain missed cases. Case ascertainment was estimated to be 82%. Among 733 patients identified, 597 (81%) enrolled, and 589 remaining on insulin were eligible for long-term follow-up (20,21).

Follow-up during the 20 years after diabetes diagnosis included biannual or annual questionnaires for diabetes management and periodic clinical examinations, including blood samples and fundus photographs. Details on retinopathy during the first 14 years were published previously (6,21). Among 462 continuing subjects, 308 participated in a 20-year exam during November 2007 through July 2011, and 305 with fundus photographs were included in the current analysis.

WDRS data collection
Twenty-year examinations were completed at three clinic sites. Pupils were dilated, and color stereoscopic photographs were captured digitally of seven standard fields in both eyes (6,21,23). Images burned to compact disc were graded (levels 10–85) by the University of Wisconsin Ocular Epidemiology Reading Center in a masked fashion according to the modified Airlie House Classification of Diabetic Retinopathy and the Early Treatment Diabetic Retinopathy Study severity of retinopathy system modified for WESDR (4). Retinopathy in the worse eye was classified as none (10–13), minimal (14–20), mild (31), mild to moderate (37), moderate (43), or moderately severe to severe nonproliferative DR (47–53) or treated DR (panretinal photocoagulation) or proliferative DR (PDR) (60–85). These were further grouped into presence or absence of DR or PDR and into three categories of severity: none or minimal (levels 10–21), mild to moderate (31–43), and vision-threatening (moderately severe or worse, ≥47).

Weight was measured on a Health-ometer (Health O Meter, Inc., Bridgeview,

IL) physician beam scale, and height was measured with a standard stadiometer height rod fixed to the scale. Seated blood pressure, after measurement of arm circumference for cuff selection, was measured in the right arm with a random zero sphygmomanometer (Hawksley and Sons, Sussex, U.K.) according to the Hypertension Detection and Follow-up Program (24) protocol 5 minutes after cuff placement and repeated after a 5-minute rest. Questionnaires were completed on diabetes self-management, including continuous subcutaneous insulin infusion (CSII, insulin pump) use or number of insulin injections per day, blood glucose checks performed each day, average daily insulin dose, other medication use, and general health and socioeconomic factors, including total years of education.

Anticoagulated whole blood samples collected at the examination were analyzed for Diabetes Control and Complications Trial (DCCT)–equivalent hemoglobin A_{1c} (HbA_{1c}) within 7 days by automated high-performance liquid chromatography at the core DCCT laboratory at the University of Minnesota (Minneapolis, MN).

Comparison with WESDR
The WESDR identified 1,210 persons with prevalent younger-onset (type 1) diabetes during 1979–1980 who were diagnosed before the age of 30 years, all of whom were using insulin and receiving their primary care within an 11-county area of southern and central Wisconsin; 996 participated in a baseline examination during 1980–1982 (4). The baseline (visit 1) and 4-, 10- and 14-year follow-up examinations (visits 2–4) in 1984–1986, 1990–1992, and 1994–1996, respectively, included color stereoscopic photographs that were taken and graded as described above and previously (4,10). We included data from the first visit falling in a duration window (17–21 years) similar to that of the WDRS ($n = 583$).

As in the WDRS, WESDR study visits included measurement of height, weight, and seated blood pressure by random zero sphygmomanometer according to the Hypertension Detection and Follow-up Program (24), as well as questions on total years of education and on diabetes self-management, with the exception that blood glucose checks per day and insulin dose were not asked about at visit 1 and lipid medication use was not asked about at visits 1 and 2 (years in which these

medications were not widely available). DCCT-equivalent HbA_{1c} values were calculated for WESDR according to a regression equation determined after split sample testing with the core DCCT laboratory at the University of Minnesota (25).

This study was performed in accordance with the Declaration of Helsinki. WDRS and WESDR study participants provided informed consent for follow-up, and the institutional review board of the University of Wisconsin approved the related protocols.

Statistical methods
Analyses were performed with the statistical software package SAS v9.2 (26). The cohorts were described by means, SDs, and percentages. The prevalences of DR and PDR at 20 years were estimated for each cohort. Diabetic retinopathy severity categories were also described. Tests for significant trends across severity category were completed by univariate linear and logistic regression models within each study cohort for glycemic control and related care variables as well as for potentially confounding factors. Data from the two cohorts were then pooled for fitting ordinal (proportional odds) logistic regression models of retinopathy severity category, where the estimated odds ratios (ORs) for higher vs. lower retinopathy are considered the same regardless of where the cutoff points are placed across the 3 categories. The model first included an indicator variable for study cohort, age at exam, and sex. Diabetes duration at exam and years of education were added to the model as significant ($P ≤ 0.05$) and having attenuated the OR for retinopathy severity in the WESDR vs. WDRS by 7 and 13%, respectively. The steps of Baron and Kenny (27) were followed to assess mediation by glycemic control (HbA_{1c}) or diabetes care or blood pressure. Interaction terms were tested in a stepwise manner. Model fit was confirmed by the Hosmer-Lemeshow goodness of fit test and χ^2 tests for the proportional odds assumption.

Sensitivity analyses were completed to assess potential participation bias at a diabetes duration of 20 years on prevalence and regression models. Analyses were repeated with weighting by the inverse of the probability of participation in the examination, thereby giving more weight to participants who resemble nonparticipants (28). Probability was estimated by logistic regression of participation status on sociodemographic

factors, diabetes care, and glycemic control at earlier durations (6,28). By similar methods, a sensitivity analysis was also completed for the WESDR cohort among those subjects examined in the diabetes duration window of 17–21 years.

RESULTS—WDRS participants in the 20 year exam were representative of the entire enrolled cohort with respect to age, sex, year and study area at diagnosis, and mean glycemic control in the first year and first 3 years after onset (data not shown), although fewer nonwhite individuals participated. Individuals were on average 11.2 years of age at diagnosis and 30.9 years of age, with a mean diabetes duration of 19.7 years, at the examination (Table 1). Participants were 49% male and 97% white. Characteristics of the WESDR group and significant differences between cohorts are also presented in Table 1. The cohorts were similar with respect to sex, race, and diabetes duration, although WESDR participants were slightly older (14.1 years at diagnosis and 33.4 years at the exam, each $P < 0.001$). Persons in the WESDR had less education than those in WDRS (13.8 vs. 15.2 years, $P < 0.001$). WESDR participants were diagnosed on average nearly two decades earlier than those in WDRS.

Diabetes management at 20 years
There were more intensive insulin management practices in WDRS than in WESDR (93.4% vs. 21.3%) with CSII or ≥ 3 insulin injections per day (multiple daily injection [MDI]) and lower HbA$_{1c}$ (8.0% vs. 9.3%) (Table 1). More individuals in WDRS were taking antihypertensive medications (28.5% vs. 18.5%), and blood pressures were higher in WESDR, especially among those taking these medications (data not shown). WDRS subjects checked blood glucose more often (mean 4.8 vs. 1.9 checks per day) and were more likely to use lipid-lowering medications (22.6% vs. 2.2%) than the WESDR subjects with blood glucose check and lipid medication data. Body weight, BMI, and insulin dose were greater in WDRS than in WESDR (Table 1).

Diabetic retinopathy
At a diabetes duration of 20 years, most individuals had evidence of some DR; however, retinopathy was less frequent and less severe in the WDRS cohort than in the WESDR cohort (Table 2). In WDRS, 92% (95% CI 89–95) showed

Table 1—Characteristics of the WDRS and WESDR study groups

Characteristic	WDRS	WESDR
N	305	583
Male	150 (49.2)	292 (50.1)
White	297 (97.4)	574 (98.6)
Age at diagnosis (years)		
Mean	**11.2 ± 7.0**	**14.1 ± 7.3**
0–4	**54 (17.7)**	**51 (8.8)**
5–9	**98 (32.1)**	**135 (23.2)**
10–14	**76 (24.9)**	**176 (30.2)**
15–19	**38 (12.5)**	**87 (14.9)**
≥20	**39 (12.8)**	**134 (23.0)**
Age at exam (years)	**30.9 ± 7.0**	**33.4 ± 7.4**
Diabetes duration (years)	19.7 ± 1.2	19.2 ± 1.4
Year of diabetes diagnosis (range)	1989 (1987–1992)	1970 (1958–1979)
Education (years)	**15.2 ± 2.6**	**13.9 ± 2.5**
HbA$_{1c}$ ($n = 537$)		
Mean (%)	**8.0 ± 1.5**	**9.3 ± 1.7**
<7%	**72 (23.7)**	**40 (7.4)**
Insulin pump (CSII)	**146 (47.9)**	**10 (1.7)**
Daily insulin injections		
Any	**157 (51.0)**	**573 (98.3)**
1–2	**18 (5.9)**	**459 (78.7)**
3	**19 (6.2)**	**66 (11.3)**
≥4	**120 (39.3)**	**48 (8.2)**
Intensive care (MDI or CSII, %)	**285 (93.4)**	**124 (21.3)**
Insulin dose, units/kg/day ($n = 417$)	**0.75 ± 0.30**	**0.70 ± 0.24**
BMI, kg/m^2 ($n = 529$)	**28.3 ± 5.9**	**26.1 ± 4.6**
Weight, kg ($n = 537$)	**83.8 ± 19.8**	**73.1 ± 14.9**
Blood glucose checks/day ($n = 378$)		
Mean	**4.8 ± 4.5**	**1.9 ± 1.7**
<1	**30 (9.8)**	**145 (38.4)**
1–2	**51 (16.7)**	**119 (31.5)**
≥3	**224 (73.4)**	**114 (30.2)**
Systolic BP (mmHg, $n = 531$)	122 ± 13	125 ± 19
Diastolic BP (mmHg, $n = 530$)	77 ± 9	79 ± 11
Antihypertensive medication	87 (28.5)	108 (18.5)
Lipid-lowering medication ($n = 358$)	**69 (22.6)**	**8 (2.2)**

Data are mean ± SD or n (%) unless otherwise specified. Boldface type indicates significant ($P < 0.01$) differences between study groups. Variables with missing data in WESDR group are noted with available n in parentheses. BP, blood pressure.

any DR, compared with 97% (95% CI 96–99) in WESDR. Only 10% (95% CI 7–14) showed evidence of PDR or treated DR in WDRS vs. 36% (95% CI 32–40) in WESDR. Weighting by inverse participation probability affected the prevalence estimates of DR and PDR in WDRS (<0.4 and 1.4%) and WESDR (<0.2 and 0.7%) little. The majority of WDRS participants displayed no DR or minimal DR (34%) or mild to moderate (48%) nonproliferative DR; 18% in WDRS had vision-threatening preproliferative or proliferative levels vs. 43% in WESDR.

Retinopathy severity is further described in Table 3. Significant trends were noted for correlation of less

education and greater diabetes duration with increasing retinopathy severity in each cohort. Trends for lower HbA$_{1c}$ and related factors, including more intensive insulin care and more blood glucose checking, were observed with decreasing retinopathy severity in both WDRS and WESDR cohorts. Blood pressures and use of antihypertensive medications increased with increasing severity category in both cohorts. A greater proportion of males was noted with increasing retinopathy severity in both cohorts, but the trend was only significant in the WESDR group. There was no effect of race on retinopathy outcome in either of the primarily non-Hispanic white cohorts.

Table 2—DR in the WDRS and WESDR studies at diabetes duration of 20 years

Retinopathy	WDRS			WESDR		
	n	%	95% CI	n	%	95% CI
Any retinopathy (DR)	281	92.1	89.1–95.2	567	97.2	95.9–98.5
None (10–13)	24	7.9	4.8–10.9	16	2.7	1.5–4.2
Nonproliferative DR	249	81.6	77.3–86.0	375	64.3	62.2–70.0
Minimal (14, 15, 20)	80	26.2	21.3–31.2	78	13.4	10.6–16.1
Mild (31)	59	19.3	14.9–23.8	50	8.6	6.3–10.8
Mild to moderate (37)	52	17.0	12.8–21.3	102	17.5	14.4–20.6
Moderate (43)	35	11.5	7.9–15.1	84	14.4	11.6–17.3
Moderately severe to severe (47, 53)	23	7.5	4.6–10.5	45	7.7	5.6–9.9
PDR or treated DR (≥60)	32	10.5	7.1–13.9	208	35.7	31.8–39.6

DR grade levels are noted in parentheses.

Ordinal logistic regression models for the three retinopathy severity categories confirmed higher, unadjusted average odds of more severe retinopathy in the WESDR era than in the WDRS era (OR 3.3 [95% CI 2.5–4.3]). With adjustment for age, sex, diabetes duration, and education, the OR was reduced to 3.0 (95% CI 2.2–4.0) (Table 4). The inclusion of 20-year HbA$_{1c}$ in the model further reduced the OR for WESDR vs. WDRS to 2.2 (95% CI 1.6–3.0). Intensive insulin care, insulin dose, and blood glucose checks were not significantly related to retinopathy once HbA$_{1c}$ was included in the model. Including blood pressure in the adjusted model minimally reduced the OR for WESDR vs. WDRS (from 3.0 to 2.9). No interaction terms were significant, and weighting for participation did not affect the final results.

CONCLUSIONS—The frequency and severity of diabetic retinopathy after a diabetes duration of 20 years was lower for individuals with type 1 diabetes diagnosed in a more recent era. This result extends our previous findings of a lower than expected prevalence of retinopathy at a diabetes duration of 4–14 years (6)

and is consistent with findings of several other studies (8–10). A similar decline in diabetes-related macular edema has also been suggested (29). In WDRS, only 12% of individuals had evidence of macular edema (4% with clinically significant edema) at 20 years (T.J.L., unpublished observations). This provides support that diabetes care is having a "positive and sustained influence on diabetes complications" (15).

Many of the recent reports on individuals followed up for longer durations of type 1 diabetes come from clinic-based studies in Europe (8,9), and only few are truly population based (11,30,31). Further, very little data exist on retinopathy prevalence among those with a diabetes duration of ≥20 years and a diagnosis after 1980, especially for type 1 diabetes alone (32).

More intensive diabetes care from early diabetes on appears to have changed the prognosis for individuals whose diagnoses were made in the current era of diabetes care (7,9,33). CSII or multiple daily insulin injections, more frequent blood glucose checking, and rapid- or prolonged-acting insulin analogs are improvements not available to the WESDR cohort during earlier diabetes durations, and for some even by a duration of 20

Table 3—Characteristics by DR category in the WDRS and WESDR study groups at diabetes duration of 20 years

Characteristic	WDRS			WESDR		
	None or minimal	Mild to moderate	Vision threatening	None or minimal	Mild to moderate	Vision threatening
N (%)	104 (34.1)	146 (47.9)	55 (18.0)	94 (16.1)	239 (40.5)	253 (43.4)
Male (%)	45.2	48.0	60.0	**40.4**	**47.5**	**56.1**
White (%)	99.0	97.3	94.5	100.0	98.3	98.4
Age at diagnosis (years)	11.4 ± 7.9	11.4 ± 6.8	10.2 ± 5.8	13.9 ± 7.7	14.3 ± 7.5	14.1 ± 6.9
Age at exam (years)	30.9 ± 8.1	31.1 ± 6.6	30.1 ± 5.7	32.8 ± 8.0	33.5 ± 7.7	33.4 ± 7.0
Diabetes duration (years)	**19.5 ± 1.1**	**19.7 ± 1.2**	**19.9 ± 1.2**	**18.9 ± 1.4**	**19.2 ± 1.3**	**19.4 ± 1.4**
Education (years)	**15.8 ± 2.4**	**15.1 ± 2.4**	**14.3 ± 2.8**	**14.4 ± 2.8**	**14.0 ± 2.8**	**13.5 ± 2.3**
HbA$_{1c}$ (%, n = 537)						
Mean	**7.6 ± 1.3**	**8.0 ± 1.4**	**8.8 ± 1.7**	**8.7 ± 1.7**	**9.1 ± 1.6**	**9.7 ± 1.7**
< 7% (%)	**34.0**	**18.5**	**18.2**	**11.1**	**9.5**	**4.2**
Intensive care (MDI or CSII), %	97.1	93.1	87.3	30.8	19.9	19.0
Insulin dose (units/kg/day, n = 417)	**0.68 ± 0.25**	**0.77 ± 0.28**	**0.82 ± 0.39**	**0.65 ± 0.17**	**0.70 ± 0.22**	**0.72 ± 0.27**
Blood glucose checks/day (n = 471)						
Mean	**5.8 ± 5.7**	**4.2 ± 3.6**	**4.2 ± 3.9**	**2.3 ± 2.0**	**1.4 ± 1.7**	**1.3 ± 1.4**
≥3 (%)	**80.8**	**71.9**	**63.6**	**43.0**	**22.7**	**18.0**
Systolic BP, mmHg (n = 531)	**119 ± 11**	**122 ± 12**	**129 ± 15**	**117 ± 15**	**123 ± 16**	**130 ± 22**
Diastolic BP, mmHg (n = 530)	**75 ± 9**	**76 ± 9**	**82 ± 8**	**72 ± 9**	**78 ± 10**	**82 ± 12**
Antihypertensive medication use (%)	**24.0**	**26.7**	**41.8**	**5.3**	**13.6**	**28.1**

Data are mean ± SD except as indicated. Boldface type indicates significant test for trend P values (P < 0.05), determined within study by linear regression for continuous and logistic regression for dichotomous variables modeled on DR category (1–3). Variables with missing data in WESDR group are noted with available n in parentheses. BP, blood pressure.

Table 4—ORs and 95% Wald CIs from ordinal logistic regression analysis modeling the odds of diabetic retinopathy severity by study cohort (n = 819)

Variable	(1) Univariate	(2) Adjusted	(3) With HbA$_{1c}$	(4) With BP	(5) With HbA$_{1c}$ and BP
WESDR study cohort	3.33 (2.52–4.39)	3.01 (2.24–4.04)	2.23 (1.63–3.03)	2.88 (2.13–3.88)	2.21 (1.62–3.02)
Age (per 1 year)		1.00 (0.98–1.02)	1.00 (0.98–1.02)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
Male		1.42 (1.10–1.85)	1.40 (1.08–1.83)	1.10 (0.84–1.45)	1.09 (0.83–1.44)
Duration (per 1 year)		1.17 (1.06–1.30)	1.21 (1.09–1.34)	1.18 (1.06–1.31)	1.21 (1.08–1.34)
Education (per 1 year)		0.88 (0.83–0.93)	0.90 (0.85–0.95)	0.89 (0.84–0.94)	0.90 (0.86–0.96)
HbA$_{1c}$ (per 1%)			1.34 (1.23–1.47)		1.31 (1.20–1.43)
Systolic BP (per 3 mmHg)				1.04 (1.00–1.07)	1.04 (1.00–1.08)
Diastolic BP (per 3 mmHg)				1.12 (1.07–1.18)	1.11 (1.05–1.17)

Data are ORs (95% CIs). Models are represented in columns as follows: (1) model with study cohort only; (2) model 1 with adjustment for age, sex, diabetes duration, and subject's total years of education; (3) model 2 with adjustment for HbA$_{1c}$; (4) model 2 with adjustment for systolic and diastolic blood pressures; (5) model 2 with adjustment for HbA$_{1c}$ and blood pressures (final model). Per unit change used in calculating ORs is noted for predictive variables in parentheses. BP, blood pressure.

years (34). Shortly after the WDRS subjects were diagnosed, the benefits of intensive therapy, especially when started earlier in the course of type 1 diabetes, were proved to reduce the risk of diabetes complications (35). WESDR participants included in this investigation were at 14–35 years after diabetes onset at the time of the first DCCT report.

Contemporary data on diabetes management practices of individuals with longer type 1 diabetes duration in the U.S. are scarce. Diabetes management in the WDRS cohort at 20 years was similar to that recently reported among both the conventional and intensively treated arms of the primary prevention group of the DCCT at a mean diabetes duration of 24 years, where approximately 50% were using insulin pumps, 50% were using MDI, and 60% were checking blood glucose 4 or more times daily (34). HbA$_{1c}$ levels were also similar in the conventional, intensive, and WDRS groups, at 7.7%, 7.8%, and 8.0%, respectively. Consistent with our finding of less severe retinopathy among those showing better diabetes management, the prevalence of PDR was 4.4% in the intensively treated group and 12.7% in the group originally treated by conventional methods (34).

Better glycemic control was the strongest predictor for decreasing severe retinopathy with time in some previous reports (7,9); however, current HbA$_{1c}$ only partially explained the difference in retinopathy between the cohorts. The stability or level of glycemic control during earlier diabetes durations may be as or more important in setting the course of retinopathy even through 20 years (13). Although data on early glycemic control are available for WDRS, the cross-sectional design of WESDR precluded the collection of such data, and an investigation of its role cannot be included in our comparison. In general, the difference in retinopathy we found between groups was of a magnitude consistent with that expected with a 1.3% difference in HbA$_{1c}$. Very likely other aspects associated with attempting and achieving better glycemic control also contributed to the lower retinopathy severity in the later era. The significance of higher education in our model, even after adjustment for glycemic control, may represent the additional impact of better self-care practices, better access to care, ability to afford testing supplies, or health literacy, all of which may result from better socioeconomic status (36) and are otherwise unmeasured in the current analysis. It may be noted that the DCCT was a trial of management and not of the impact of low HbA$_{1c}$ in isolation. Despite this, the aspects of diabetes management consistently measured in both studies did not further explain the difference in retinopathy outcome. Data on diabetes management are by nature self-reported and potentially subject to reporting bias. Finally, some aspects of management, such as the use of insulin pumps, were so strongly associated with diagnostic era that they could not be formally tested as mediators.

Higher blood pressure has previously been linked to progression of retinopathy (10), and more frequent or earlier use of angiotensin converting enzyme inhibitors in the WDRS cohort may have resulted in lower blood pressures. Hovind et al. (8) found lower blood pressures and increased treatment and shorter time to initiation with angiotensin converting enzyme inhibitors with later calendar year of type 1 diabetes diagnosis. Of note, antihypertensive medication use appeared to be associated with worse retinopathy outcome, reflecting that those with higher blood pressures both used medications and were at greater risk for progression. Less stringent blood pressure treatment goals in the WESDR era likely contributed to the higher treated blood pressures in this cohort. Confounding by indication and the change in indication precluded an investigation of potential mediation by these medications.

Although BMI differed between the cohorts, it had little effect on retinopathy outcome, remaining nonsignificant in regression analysis. Inclusion of HbA$_{1c}$ in the model and greater BMI in WDRS associated with achieving lower HbA$_{1c}$ could have concealed an independent effect. Obesity and insulin resistance–related factors, perhaps better captured by alternative measures, have previously been found to be associated with complications risk in some reports in type 1 diabetes (37–39), especially pertaining to kidney and cardiovascular disease risk (38,39); this constitutes an area of future research in the WDRS and is outside the scope of this report. On a related note, unmeasured factors involving health behaviors, such as diet and exercise, may have improved with time and impacted our findings.

More recently noted increases in the incidence of type 1 diabetes among younger individuals (40) could have also contributed to the greater severity of retinopathy seen in an older era. Indeed, a lower average age at diagnosis in the WDRS cohort was found, and it resulted in a slightly greater postpubertal duration among the WESDR cohort (data

not shown). This variation, however, had little impact on the reported difference in outcome between the study periods.

The WDRS and the WESDR provided a unique opportunity to compare outcomes of individuals with type 1 diabetes across time. Few population-based studies exist that followed individuals from diagnosis for such a long period. The overlapping study area and the same approach to definition of retinopathy also reduced bias from differing methodologies and demographics. Still, limitations do exist. The current analysis was cross-sectional and captured the point prevalence at 20 years, previously determined as the time by which nearly all individuals would have some level of DR. Those who chose not to participate in the examination or were no longer continuing WDRS subjects could have displayed more severe retinopathy. This was not seen, however, in questionnaire responses regarding whether participants had ever been told of having diabetes-related eye changes or disease by a health care provider. Further, weighting for participation probability based on baseline characteristics of the original cohort of 589 showed that prevalence estimates changed very little from original results.

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