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The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII. The Twenty-Five-Year Progression of Retinopathy in Persons with Type 1 Diabetes

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Abstract

Objective—To examine the 25-year cumulative progression and regression of diabetic retinopathy (DR) and its relation to various risk factors.

Design—Population-based study.

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

Methods—Stereoscopic color fundus photographs were graded using the modified Airlie House classification and the Early Treatment Diabetic Retinopathy Study retinopathy severity scheme.

Main Outcome Measures—Progression and regression of DR status.

Results—The 25-year cumulative rate of progression of DR was 83%, progression to proliferative DR (PDR) was 42%, and improvement of DR was 18%. Progression of DR was more likely with less severe DR, being male, having higher glycosylated hemoglobin, an increase in the glycosylated hemoglobin level, and an increase in diastolic blood pressure level from the baseline to the 4-year follow-up. Increased risk of incidence of PDR was associated with more severe baseline DR, higher glycosylated hemoglobin, and greater body mass index at baseline, and an increase in the glycosylated hemoglobin between the baseline and 4-year follow-up examination. Lower glycosylated hemoglobin and being male, as well as decreases in glycosylated hemoglobin and diastolic blood pressure over the first 4 years of follow-up, were associated with improvement in DR.

Persons diagnosed most recently with similar duration of diabetes had lower prevalence of PDR independent of glycosylated hemoglobin level, blood pressure level, and presence of proteinuria.

Conclusions—These data show relatively high 25-year cumulative rates of progression of DR and incidence of PDR. The lower risk of prevalent PDR in more recently diagnosed persons possibly reflects improvement in care over the period of the study.

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Diabetic retinopathy (DR) is an important cause of visual impairment, especially in persons 25–65 years of age.[1–3] While epidemiological studies have described the incidence of DR.[1,4–26] and relationships to various risk factors, many of these studies have been in persons with type 2 diabetes and few have examined these relationships over a long period of time.[11,20–26] Even fewer studies have examined regression of DR and associated factors.[11] Recent changes in rates of progression and improvement of DR would be expected with the more widespread use of intensive glycemic and blood pressure control.[1,15,27–29] In this report, we extend our previous observations by describing the 25-year progression and regression of DR, the incidence of proliferative diabetic retinopathy (PDR), and changes in the prevalence of PDR in a large cohort of persons with type 1 diabetes mellitus participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).[11]

METHODS AND MATERIALS

Study Population

The population, which has been described in previous reports,[9–11,30–33] consisted of a sample selected from 10,135 diabetic patients who received primary care in an 11-county area in southern Wisconsin from 1979 to 1980. This sample was composed of all "younger-onset" and a duration stratified sample of "older-onset" persons. The analyses in this report are limited to the group of younger-onset persons, all of whom were taking insulin and had been diagnosed before 30 years of age (n = 1210). There were 996 persons in this group who participated in the baseline examination (1980 to 1982),[31] 903 in the 4-year follow-up,[9] 816 in the 10-year follow-up,[10] 667 in the 14-year follow-up,[11] 567 in the 20-year follow-up,[33] and 520 in the 25-year follow-up (Figure 1). Nine hundred and fifty-five participated at baseline and at least one of the 4 follow-up examinations or died before the first follow-up examination (n=64). The reasons for nonparticipation and comparisons between participants and nonparticipants at baseline and the 4-, 10-, and 14-year follow-ups have been presented elsewhere.[9–11,31,33] Retinopathy data were not collected at the 20-year follow-up, so information from that examination is not included in this report. For the 25-year follow-up, the reasons for nonparticipation are presented in Figure 1. Mean (± standard deviation [SD]) and median times between the baseline and 25-year follow-up examinations were 25.1 ± 0.6 years and 25.1 years, respectively.

Procedures

The baseline and follow-up examinations were performed in a mobile examination van in or near the city where the participants resided. All examinations followed a similar protocol that was approved by the institutional human subjects committee of the University of Wisconsin and conformed to the tenets of the Declaration of Helsinki. The pertinent parts of the ocular and physical examinations included measuring weight, height, and blood pressure,[34] dilating the pupils, taking stereoscopic color fundus photographs of seven standard fields[35,36] (not done at 20 year follow-up), performing a semiquantitative determination of protein levels in the urine using Labstix (Ames, Elkhart, IN), and determining blood glucose and glycosylated hemoglobin A1 levels from a capillary blood sample at baseline, 4-, 10- and 14-yr follow-up and glycosylated hemoglobin A1c from venous blood at the 20- and 25-year follow-up (Quick Step Fast Hemoglobin Test System. Akron, OH: Isolab).[37] The normal range for glycosylated hemoglobin A1 was 4.6% to 7.9%. Its intra-assay coefficient of variation was 2.4%. The WESDR glycosylated hemoglobin A1 microcolumn results compare with the Diabetes Control and Complications Trial (DCCT) glycosylated hemoglobin A1c results as follows: DCCT = 0.003 + 0.935 (WESDR).[38]

A structured interview was conducted by the examiners that included questions about specific medications for control of hyperglycemia and blood pressure, the number of aspirin used during

the 30 days before the baseline examination, and smoking history. If there was any question about medication usage, it was verified by a physician's report.

Grading Protocol

Grading protocols have been described in detail elsewhere[9,39] and are modifications of the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification of DR.[40,41] Interobserver and intraobserver variations and the validity of the systems have been evaluated, and the results have been presented elsewhere.[9,39,41,42]

Definitions

For each eye, the maximum grade in any of the seven standard photographic fields was determined for each of the lesions and used in defining the “retinopathy levels” as follows:[10,41]

Level 10:	No retinopathy.
Level 21:	Microaneurysms (MAs) only or retinal hemorrhages (H) or soft exudates in the absence of MAs.
Level 31:	MAs and one or more of the following: venous loops 31 μm or greater; questionable soft exudate, intraretinal microvascular abnormalities (IRMA) or venous beading; and retinal H.
Level 37:	MAs and one or more of the following: hard exudate and soft exudate.
Level 43:	MAs and one or more of the following: H/MAs equaling or exceeding those in Standard Photo (SP) 1 in four or five fields; H/MAs equaling or exceeding those in SP 2A in one field; and IRMA in one to three fields.
Level 47:	MAs and one or more of the following: both IRMA and H/MA characteristics from level 43; IRMA in four or five fields; H/MAs equaling or exceeding those in SP 2A in two or three fields; and venous beading in one field.
Level 53:	MAs and one or more of the following: any two or three characteristics from level 47; H/MAs equaling or exceeding those in SP 2A in four or five fields; IRMA equaling or exceeding those in SP 8A; venous beading in two or more fields.
Level 60:	Fibrous proliferations only.
Level 61:	No evidence of levels 60 or 65 but scars of photocoagulation either in “scatter” or confluent patches, presumably directed at new vessels.
Level 65:	PDR less than DR Study high-risk characteristics (DRS-HRC). Lesions as follows: new vessels elsewhere (NVE); new vessels on or within 1 disc diameter (NVD) of the disc graded less than SP 10A; or preretinal (PRH) or vitreous hemorrhage (VH) less than 1 disc area (DA).
Level 71:	DRS-HRC. Lesions as follows: VH and/or PRH equaling or exceeding 1 DA; NVE equaling or exceeding one-half DA with VH and/or PRH; NVD less than SP 10A with VH and/or PRH; and NVD equaling or exceeding SP 10A.
Level 75:	Advanced PDR, lesions as follows: NVD equaling or exceeding SP 10A with VH and/or PRH.
Level 85:	End-stage PDR, lesions as follows: macular obscured by VH and/or PRH; retinal detachment at center of macula; phthisis bulbi; and enucleation secondary to complications of DR.

The DR level for a participant was derived by concatenating the levels for the two eyes, giving the eye with the higher level greater weight. This scheme provided a 15-step scale (10/10, 21/<21, 21/21, 31/<31, 31/31, 37/<37, 37/37, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60+/<60+, and 60+/60+) when all levels of PDR are grouped as one level. For purposes of classification, if the DR severity could not be graded in an eye, it was considered to have a score equivalent to that in the other eye.

The cumulative incidence of any DR was estimated from all persons who had no DR at the baseline examination (severity level 10/10) and who participated in the follow-up examination

(s). Incidence of PDR was estimated from all persons who were free of this complication at the baseline examination. For persons with no or only nonproliferative diabetic retinopathy (NPDR), progression was defined as the first instance of an increase in the severity of DR by two steps or more from the level at any of the previous follow-up examinations. Improvement in DR was defined in persons with levels 21/21 to 53/53 as the first instance of a 2-step or more decrease in the severity of DR from the level at any of the previous follow-up examinations. Thus, analyses for progression and improvement were restricted to subjects who could potentially progress or improve by two steps. Progression was examined separately in persons who had PDR at the baseline examination because many of these individuals had received panretinal photocoagulation treatment.

Age was defined as the age at the time of the baseline examination. Age at diagnosis of diabetes was defined as the age at the time the diagnosis was first recorded by a physician on the patient's chart or in a hospital record. The duration of diabetes was that period between the age at diagnosis and the age at the baseline examination. Changes in glycosylated hemoglobin and blood pressure were defined as the difference between the value at the 4-year examination and the value at baseline.

Systolic and diastolic blood pressures were the average of the two measurements taken according to the protocol of the Hypertension Detection and Follow-Up Program protocol.[34] Hypertension was defined as a mean systolic blood pressure ≥ 160 mmHg and/or a mean diastolic blood pressure ≥ 95 mmHg or a history of antihypertensive medication at the time of examination in individuals ≥ 25 years of age or a mean systolic blood pressure of ≥ 140 mmHg and/or a mean diastolic blood pressure of ≥ 90 mmHg, and/or a history of antihypertensive medication at the time of examination in younger persons.

A person was classified as a never smoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime, as an ex-smoker if he/she smoked more than this number of cigarettes in his/her lifetime but had stopped smoking before the examination, and as a current smoker if he/she had not stopped. Pack-years smoked was calculated as the number of cigarettes smoked per day divided by 20, multiplied by the number of years of smoking from the time of diagnosis of diabetes. Body mass index (BMI) was defined as weight in kg divided by the height in m^2. Proteinuria was defined as urine protein concentration of 30 mg/dL or greater as measured by Labstix.

Statistical Methods

Cumulative 25-year incidence and progression rates were calculated with a competing risk approach (a modification of the Kaplan-Meier approach) to account for censored observations due to missed examinations and the competing risk of death.[43] Estimated incidence and progression rates between examinations were converted to average annual rates using the formula: $1-(1-p_n)^{1/n}$, where n is the number of years between examinations and p_n is the cumulative rate between examinations.

For multivariable analyses, we used generalized linear models for the binary outcomes (incidence, progression and improvement during the examination interval) using the complementary log-log link function to estimate underlying continuous-time proportional hazard models while accounting for the varying follow-up times between examinations. For these analyses, duration of diabetes was the time variable and the baseline hazard was assumed to be piecewise constant within 5-year bands of diabetes duration starting at 10 years and continuing to > 40 years. Hazard ratios estimates were calculated by exponentiation of estimated coefficients. PROC NLMIXED of SAS version 9.1 (Cary, NC) was used for these analyses.

Variables to include in the multivariable analyses were selected in stepwise fashion from the following list: age at diagnosis, sex, glycosylated hemoglobin, change in glycosylated hemoglobin, systolic and diastolic blood pressure, change in systolic and diastolic blood pressure, hypertension, gross proteinuria, BMI, and severity of retinopathy at baseline. Continuous variables were included as linear terms. Additional models which included smoking history, pack years smoked after diagnosis of diabetes, and history of number of aspirin consumed in the 30 days prior to the baseline examination were estimated for those 18 years of age or older at baseline. Three sets of models were considered: 1) models including only baseline characteristics; 2) models including both baseline and 4-year change characteristics (using the 21 years of follow-up from the 1st follow-up examination); and 3) models using time-varying covariates updated at each follow-up examination (i.e., for each time interval in which a subject participated, the values of the risk factors at the beginning of the interval were used).[44]

RESULTS

Characteristics of the Cohort

Characteristics at the baseline examination of those who participated in the 25-year follow-up, those who did not participate because they could not be located or they refused, and those who had died in the 11-year interval between the 14- and 25-year examinations are given in Table 1. With the exception of less education, there were no significant differences in characteristics of those who participated compared to those who survived but did not participate. The 120 younger-onset persons who had died were older and had longer duration of diabetes, higher glycosylated hemoglobin, more proteinuria, higher systolic blood pressure, greater BMI, more pack years smoked, more severe retinopathy, and poorer visual acuity than those who participated (Table 1). They also had a higher frequency of panretinal photocoagulation (data not shown) than those who participated.

Factors Associated with the Cumulative Incidence and Progression of DR

The 25-year cumulative incidence of DR in the population accounting for the competing risk of death was 97%. We excluded this endpoint in all further analyses. The 25-year cumulative rate of progression of DR was 83% (95% CI 80 to 86%, Table 2). Cumulative rates of progression decreased or remained constant while the competing risk of death increased with age and duration at baseline (Table 2). The estimates of the annual rate of progression of DR over the four study intervals are presented in Figure 2. The annualized estimates are similar for progression of DR except for the last period where it is markedly lower.

In univariate analyses, being male, having a higher glycosylated hemoglobin level and greater BMI at baseline were significantly associated with progression of DR (Table 3). Systolic or diastolic blood pressure, hypertension, gross proteinuria, smoking status, pack-years smoked while having diabetes, and education level at baseline were not associated with progression of DR (Table 3).

Time-varying covariate analyses generally showed similar associations to those found with analyses using only baseline covariates (data not shown) with the exception of stronger associations of progression of DR with diastolic blood pressure (Hazard Ratio [HR] per 10 mmHg 1.13, 95% Confidence Interval [CI] 1.05, 1.23, $P = .002$).

Multivariate analyses showed that being male, having higher glycosylated hemoglobin, greater BMI, and having less severe DR at baseline were associated with the progression of DR over 25 years (data not shown). When DR retinopathy severity was not entered into the model,

systolic blood pressure, hypertension status and gross proteinuria were significantly associated with progression to PDR (Table 4).

Factors Associated with the Cumulative Incidence of PDR

The 25-year cumulative incidence of PDR (accounting for competing risk of death) was 42% (95% CI 39 to 46%, Table 2), 16% of whom developed Diabetic Retinopathy Study high risk characteristics (DRS-HRC). The cumulative incidence remained relatively constant across ages and durations. This is likely due to the increase in the competing risk of death with increasing age or duration (Table 2). The estimates of the annual rate of incidence of PDR over the four study intervals are presented in Figure 2. There was an increase in the estimated annualized incidence of PDR from the first four years of the study to the following six years; it then fell during the next four years of follow-up and continued to fall further in the last 11 years of the study.

In univariate analyses, glycosylated hemoglobin, gross proteinuria, DR severity, systolic and diastolic blood pressure, hypertension status, and BMI at baseline were associated with incidence of PDR while sex, smoking status and education were not (Table 4). Time-varying covariate analyses were consistent with analyses using only baseline measurements except that the associations of hypertension status and BMI with progression to PDR were no longer statistically significant (data not shown).

Multivariate analyses showed that having more severe DR, higher glycosylated hemoglobin, and greater BMI at baseline were associated with progression to PDR over 25 years (data not shown). When DR retinopathy severity was not entered into the model, systolic blood pressure and gross proteinuria were significantly associated with progression to PDR (Table 4).

In a separate multivariate analysis, controlling for duration, glycosylated hemoglobin, diastolic blood pressure, BMI, and sex, a 1% absolute increase in glycosylated hemoglobin between baseline and the 4-yr follow-up was associated with progression of PDR over 21 years (HR 1.18, 95% CI 1.11, 1.25, $P < .001$). The relationship with change in diastolic blood pressure (HR per 10 mmHg 1.12, 95% CI 0.98, 1.28, $P = .09$) was of borderline statistical significance.

Progression of PDR

Of the 227 persons who were found to have PDR in at least one eye at baseline, 73.6% (n = 167) died during the 25-year follow-up. In the 103 persons with DRS-HRC or worse in at least one eye, 81.6% (n = 84) died by 25 years, significantly higher ($P = .001$) than in the 124 persons without DRS-HRC (66.9%, n = 83).

Of the 95 persons with active PDR without DRS-HRC in at least one eye (level 65) at baseline who were reexamined, 30.5% (n = 29) were found to have PDR with at least DRS-HRC (levels 71 and 75) in at least one eye, and 7.4% (n = 7) were found to have progressed beyond DRS-HRC and to have lost vision in at least one eye (level 85) by the 25-year follow-up. New panretinal photocoagulation treatment was observed in 89.6% (n = 26) and new vitrectomy treatment in 25.0% (n = 7) of this group. Of the 38 persons with DRS-HRC in at least one eye who were reexamined, 39.5% (n = 15) had progressed to level 85 in at least one eye and 13.2% (n = 5) in both eyes. New panretinal photocoagulation treatment was seen in 100% (n = 14) and vitrectomy procedure in 60% (n = 9).

Changes in Prevalence of PDR by Year at Diagnosis

Prevalence of PDR by year of diabetes diagnosis and duration of diabetes is presented in Figure 3. Persons diagnosed in 1975–80 had statistically significantly lower prevalence than in groups diagnosed in earlier periods ($P < .001$). This difference remained while controlling for

glycosylated hemoglobin, systolic or diastolic blood pressure, and presence of proteinuria (data not shown).

Factors Associated with the Cumulative Rate of Improvement of DR

The 25-year cumulative rate of improvement in DR (accounting for competing risk of death) was 18% (95% CI 14 to 21%) (Table 2). Improvement was not linearly related to age or duration of diabetes at baseline. The annualized rates of improvement dropped from the first to the second period of observation and remained similar in the last two periods of observation (Figure 2).

In univariate analyses, being male, having higher glycosylated hemoglobin, and being a current smoker compared to never smoking were associated with improvement in DR, while age at diagnosis of diabetes, systolic or diastolic blood pressure, hypertension status, education level, BMI, or history of aspirin use were not (Table 5). Time-varying covariate analyses were consistent with the above analysis for glycosylated hemoglobin findings (HR per 1% 0.78, 95% CI 0.70, 0.86, P < .001); however, higher systolic blood pressure (HR per 10 mmHg 0.87, 95% CI 0.72, 0.95, $P = .006$), diastolic blood pressure (HR per 10 mmHg 0.84, 95% CI 0.72, 0.98, $P = .03$), and presence of gross proteinuria (HR 0.47, 95% CI 0.28, 0.77, $P = .003$) were associated with less likelihood of improvement of DR.

Multivariate analyses showed that being male, having less severe DR (borderline significance), and having lower glycosylated hemoglobin at baseline were associated with the improvement in DR over 25 years (Table 5). In a separate multivariate analysis, controlling for sex, glycosylated hemoglobin, diastolic blood pressure, and retinopathy severity level, a 1% absolute increase in glycosylated hemoglobin between baseline and the 4-yr follow-up (HR 0.85, 95% CI 0.77, 0.95, $P = .003$) and a 10 mmHg increase in the diastolic blood pressure (HR 0.78, 95% CI 0.65, 0.95, $P = .01$) were associated with less improvement of DR over 21 years of follow-up.

DISCUSSION

The data reported herein provide unique population-based information regarding the 25-year cumulative rates of progression and improvement of DR and their relationship to glycemia, blood pressure, and other factors in persons with type 1 diabetes mellitus over a period of profound change in the management of this condition. The overall 25-year incidence of any retinopathy (97%), rates of progression of retinopathy (83%), and progression to proliferative retinopathy (42%) were high and the strongest most consistent relationships were with glycemia.

There are few other population-based cohorts of persons with type 1 diabetes with a similar period of follow-up to which these data can be compared.[28,45,46] Based on our findings, we estimate that over a 25-year study period, of the 515,000 to 1.3 million Americans thought at present to have type 1 diabetes, that 185,000 to 466,000 will develop PDR of whom 63,000 to 159,000 will develop PDR with DRS-HRC (NIDDK Clearing House http://www.medhelp.org/NIHlib/GF-254.html#four accessed 2/7/08). The lower prevalence of PDR in the most recently diagnosed type 1 diabetic subjects in our study and the decline in estimated annualized incident rates of PDR between the 1994–95 and 2005–06 examinations from earlier periods suggest the possibility that applying these figures to persons who currently have type 1 diabetes may overestimate the number of persons who have and will develop PDR over the next 25 years. There are few other population-based studies in which incidence data collected over a long period of time employing objective measures have been used to detect changes in prevalence or incidence of PDR. Data from a clinic-based study in Denmark showed that the incidence of PDR for a specific duration of diabetes declined for each subsequent 5-

years at year of diagnosis from 1965–69 through 1979–80.[28] This decline was associated with statistically significant trends of decreasing glycosylated hemoglobin, mean arterial blood pressure levels, and earlier treatment of hypertension in each subsequent period. The declining incidence of PDR has been found in the long-term study of another group of type 1 diabetic patients in which there was a greater than 50% reduction in incidence of PDR in the most recently diagnosed group.[45] On the other hand, in an American cohort of persons with type 1 diabetes followed in Pittsburgh, the cumulative incidence of PDR was not statistically significantly lower in more recently diagnosed persons.[46] In the WESDR, the reasons for this decline in prevalent PDR may involve better glycemic control[47] or death leading to selection of the healthiest. However, controlling for glycosylated hemoglobin levels in our study did not affect this finding. It is also possible that the decline in the prevalence of PDR over time found in our study may reflect greater exposure to health care professionals as a result of participation in the study. We think this is less likely due to intermittency of the follow-up examinations, on average, every 5 years. This information on declining prevalence and incidence of PDR is important in planning for counseling and rehabilitative services, projecting costs, measuring temporal trends, developing causal inferences, and providing sample size estimates for conducting clinical trials. For example, if there is a “true” decrease in the incidence and prevalence of PDR in persons with type 1 diabetes, there may be a need for fewer health care resources to detect and treat these individuals with panretinal and focal photocoagulation.

Glycemic control at baseline and throughout the study period was strongly related to progression and improvement of DR. This is consistent with our earlier findings and with findings from the DCCT/EDIC and other studies.[1,47–50] While controlling for other factors, a one-percentage-point decrease in the glycosylated hemoglobin A1 level from baseline to 4-year follow-up was associated with an 18% decrease in the 21-year progression to PDR and a 15% increase in improvement in our study. We found similar results in models that updated glycosylated hemoglobin and changes in it between examinations at each interval of evaluation. It is also consistent with data from the DCCT that showed that in people with type 1 diabetes, intensive glycemic control is associated with significant reduction in the progression and significant increase in improvement of established retinopathy independent of duration of diabetes and level of baseline retinopathy.[51,52] However, data from that trial showed a benefit of beginning intensive treatment with insulin and better glycemic control earlier in the course of diabetes prior to the onset of DR.

Our data show that in comparison with glycemic control, blood pressure levels were less strongly associated with the progression and improvement of DR. We had previously reported relationships between blood pressure and the progression of DR, progression to PDR, and improvement of DR at the 14-year examination that was consistent with data from other studies of persons with type 1 diabetes.[6,7,11,23,53,54] Systolic blood pressure was related to progression to PDR. While data from clinical trials have demonstrated a beneficial effect of intensive blood pressure control in persons with type 2 diabetes, this has still not been conclusively shown in persons with type 1 diabetes.[55–57] The effect of blood pressure on DR may be moot, given that intensive control of blood pressure has been shown to reduce morbidity (myocardial infarction, stroke and nephropathy) and mortality.

In the WESDR, being male was associated with a 33% higher risk of progression and a 45% lower risk of regression, independent of other risk factors. This is consistent with our previous finding of a higher prevalence of severe PDR with high risk for severe visual loss in younger-onset males (12%) compared to females (7%)[16] but not with other studies.[16,58,59] Our finding may, in part, be related to hormonal changes in men. In a nested case-control study within the WESDR, cases (n = 22) defined as subjects who progressed to proliferative or preproliferative retinopathy 6 years later had lower serum sex hormone-binding globulin than controls (n = 22) defined as subjects who had little or no progression.[60] It is also possible that unmeasured

differences in factors between men and women, e.g., atherosclerosis, might also explain these findings in the WESDR.[61]

There are many strengths of the study including a large cohort with a broad distribution of severity of retinopathy at baseline, a low refusal rate, and use of standardized protocols of measurement which included objective recording of DR using stereoscopic fundus photographs of seven standard fields. However, caution should be observed when interpreting the findings from our study. Mortality may affect the relation of risk factors to incidence of endpoints. Because glycosylated hemoglobin, blood pressure, gross proteinuria, and retinopathy severity level are significantly associated with incidence of PDR and decreased survival,[62] it is likely that the effect of death would diminish the strength of these relationships.

In summary, our data suggest that better glycemic control, and to a lesser extent blood pressure control at baseline and throughout the study, may be beneficial in reducing the incidence of PDR and in increasing the odds of improvement of DR. In addition, our data show a reduction in the prevalence of PDR in more recently diagnosed cohorts, suggesting a possible benefit of recent changes in management of diabetes on the prevalence of PDR.

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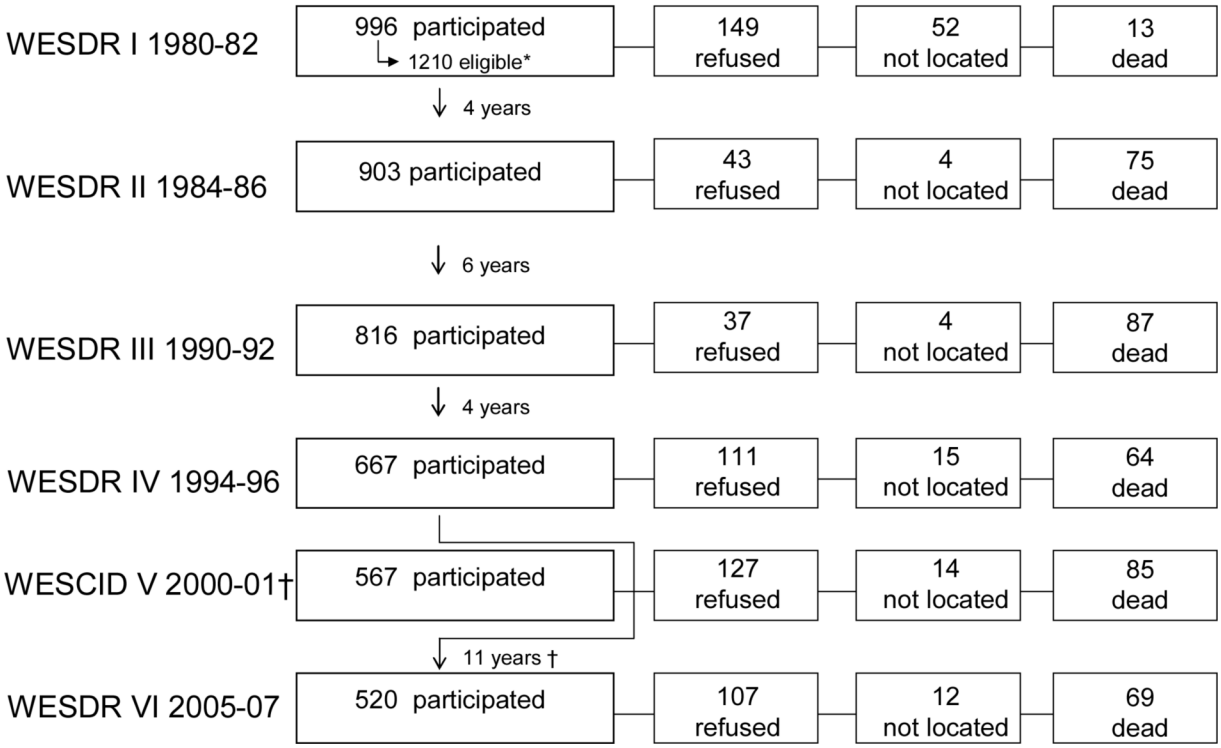

Figure 1.
Reasons for nonparticipation in the 25-year follow-up in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).
* After baseline examination, no longer contacted 178 of those eligible (excluded from W2 – W6 numbers)
† Retinopathy data not collected at Wisconsin Epidemiologic Study of Cardiovascular Disease (WESCID) in Type 1 Diabetes.

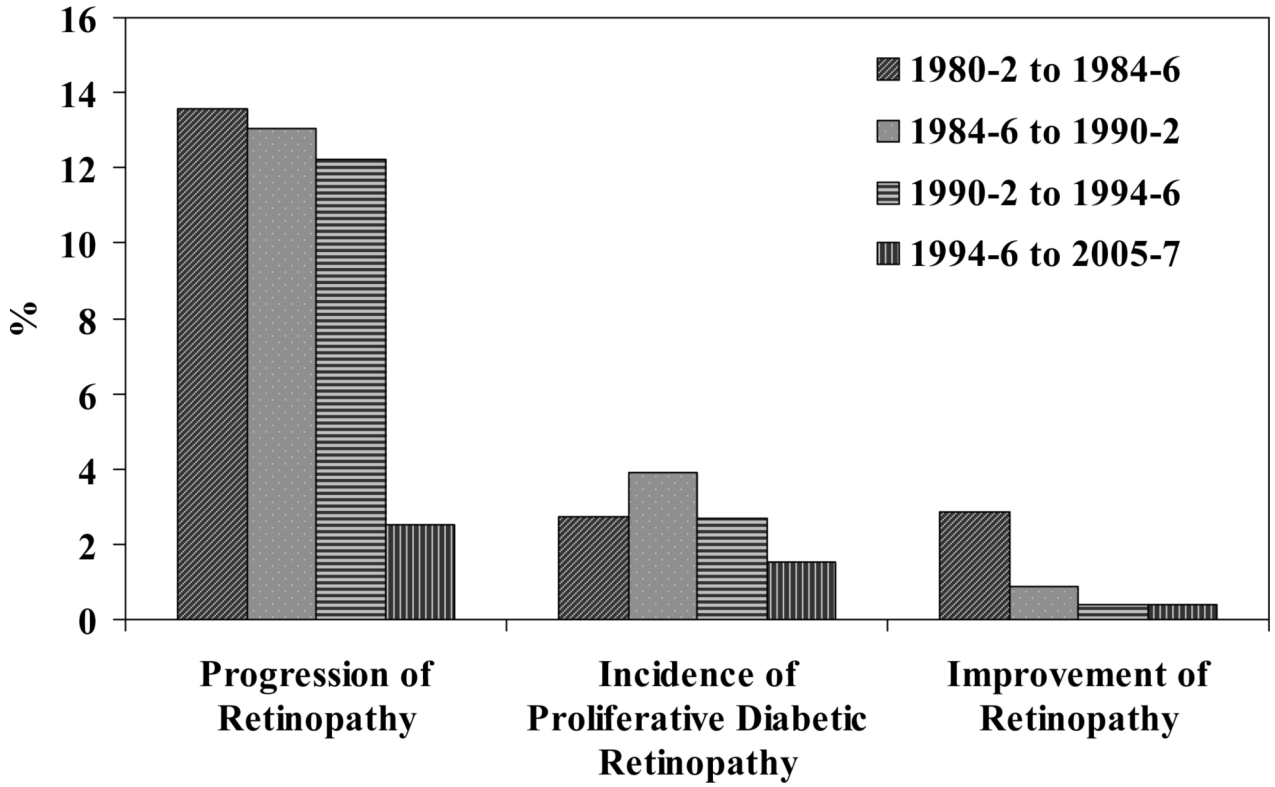

Figure 2.
Estimated annual rates for progression of diabetic retinopathy, incidence of proliferative diabetic retinopathy and improvement of diabetic retinopathy for four periods of the study.

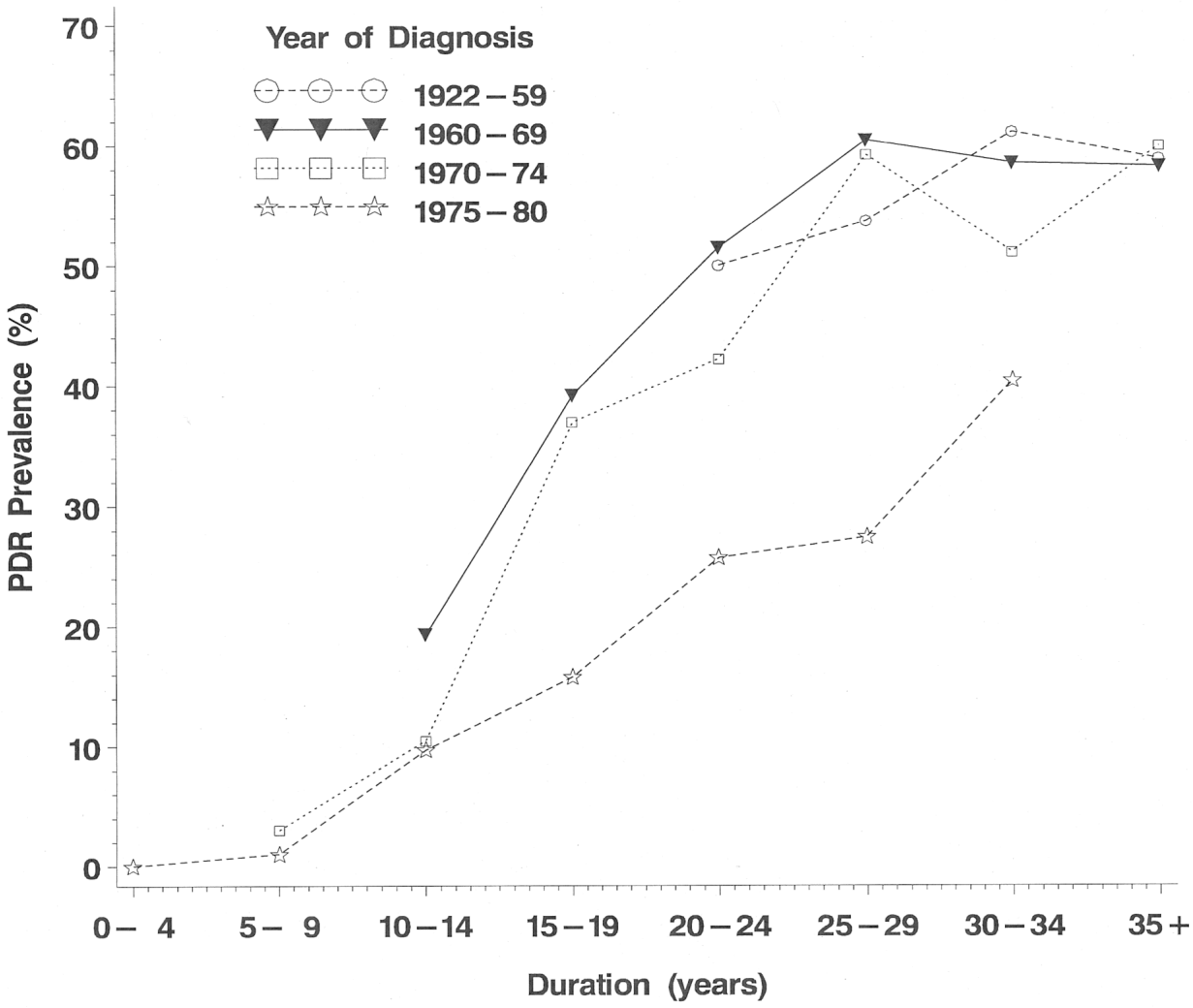

Figure 3.
Relationship of prevalence of proliferative diabetic retinopathy to duration of diabetes by period of diabetes diagnosis in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Abbreviation: PDR=proliferative diabetic retinopathy

Table 1

Selected Baseline Characteristics of Participants and Nonparticipants in the 25-Year Follow-up Examination of the Wisconsin Epidemiologic Study of Diabetic Retinopathy.

		Participants at WESDR6*		Refused or Not Located			Died Prior to WESDR6		
Baseline Characteristic	**Unit**	**N**	**Mean (SD) or%**	**N**	**Mean (SD) or%**	**P**	**N**	**Mean (SD) or%**	**P**
Age	Years	482	24.9 (9.3)	56	23.7 (11.1)	.40	120	35.2 (13.4)	<.001
Duration	Years	482	10.7 (7.1)	56	10.8 (9.4)	.94	120	20.0 (10.9)	<.001
Age at diagnosis	Years	482	14.1 (7.2)	56	12.9 (7.4)	.23	120	15.2 (8.1)	.14
Sex	Female	242	50.2	33	58.9	.22	57	47.5	.60
	Male	240	49.8	23	41.1		63	52.5	
Glycosylated hemoglobin A_1	%	458	10.5 (2.0)	54	10.7 (2.2)	.56	114	11.0 (2.0)	.04
Proteinuria	No	413	87.7	48	88.9	.80	81	70.4	<.001
	Yes	58	12.3	6	11.1		34	29.6	
Retinopathy level	10	174	36.1	26	46.4	.96	17	14.2	<.001
	21	105	21.8	11	19.6		11	9.2	
	31–37	113	23.4	5	8.9		36	30.0	
	43–53	50	10.4	2	3.6		17	14.2	
	60+	40	8.3	12	21.4		39	32.5	
Systolic blood pressure	mm Hg	481	118.4 (14.0)	56	117.3 (13.2)	.54	119	128.7 (21.3)	<.001
Diastolic blood pressure	mm Hg	480	77.0 (10.6)	56	76.9 (10.3)	.97	119	79.0 (11.4)	.07
Hypertension	No	422	87.7	48	85.7	.67	89	74.8	<.001
	Yes	59	12.3	8	14.3		30	25.2	
Smoking History†	Never	226	61.2	17	48.6	.06	59	54.1	.40
	Past	54	14.6	4	11.4		23	21.1	
	Current	89	24.1	14	40.0		27	24.8	
Pack years†	None	234	63.4	18	51.4	.14	62	56.9	.01
	<5	72	19.5	9	25.7		13	11.9	
	5–14	36	9.8	3	8.6		16	14.7	
	≥15	27	7.3	5	14.3		18	16.5	

Table 2

25-year Cumulative Rates for Progression of Retinopathy, Incidence of PDR and Improvement of Retinopathy by Age and Diabetes Duration.

	Progression of Retinopathy				Incidence of PDR				Improvement of Retinopathy			
			Cumulative Progression (%)				Cumulative Incidence (%)				Cumulative Regression (%)	
	No. at Risk	No. Events	Event	Risk of Dying Prior to Event	No. at Risk	No. Events	Event	Risk of Dying Prior to Event	No. at Risk	No. Events	Event	Risk of Dying Prior to Event
All groups	734	586	83.1	9.2	734	285	42.2	15.0	403	69	17.8	30.3
Age												
0–9 years	27	21	100.0	0.0	27	1	5.9	0.0	0			
10–14 years	80	75	95.5	1.3	80	28	43.3	9.5	5	1	20.0	0.0
15–19 years	143	126	91.7	3.7	143	55	41.6	8.5	58	7	12.3	24.5
20–24 years	132	113	87.2	3.3	132	65	51.4	6.6	86	12	14.3	12.7
25–29 years	101	86	89.3	2.3	101	45	48.1	8.0	68	11	17.3	30.4
30–34 years	103	78	80.1	6.7	103	37	39.9	13.9	59	9	16.0	31.0
35+ years	148	87	60.2	31.2	148	54	37.7	38.3	127	29	23.7	45.3
Diabetes Duration												
0–2 years	77	64	88.6	1.3	77	13	19.3	5.8	5	2	40.0	60.0
3–4 years	83	71	92.8	0.0	83	24	39.1	10.1	5	1	20.0	0.0
5–9 years	231	206	92.3	2.3	231	94	44.4	7.8	96	10	10.6	18.5
10–14 years	141	122	89.2	4.6	141	80	59.4	8.4	113	14	13.0	20.5
15–19 years	81	63	80.9	9.5	81	36	47.5	14.3	70	12	18.7	34.7
20–24 years	43	26	62.1	22.4	43	16	38.9	24.7	42	8	19.7	38.0
25–29 years	37	22	61.5	24.5	37	16	44.4	33.1	35	13	37.1	31.2
30+ years	41	12	29.3	65.2	41	6	14.6	74.8	37	9	24.7	72.5

Abbreviation: PDR=proliferative diabetic retinopathy

Table 3

Associations with Progression of Diabetic Retinopathy.

		Univariate			Multivariate*		
Risk variable	**Level**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Sex	Male	1.30	1.11, 1.54	0.002	1.33	1.11, 1.58	0.002
Age at diagnosis	10–19 yrs vs <10 yrs	1.00	0.82, 1.21	0.97			
	20–29 yrs vs <10 yrs	0.85	0.68,1.06	0.15			
Glycosylated hemoglobin A_1	Per 1%	1.29	1.24, 1.35	<.001	1.32	1.26, 1.38	<.001
Glycosylated hemoglobin A_1 quartiles	9.5–10.5 vs <9.5%	1.72	1.34, 2.21	<.001			
	10.6–12.0 vs <9.5%	2.42	1.91, 3.06	<.001			
	12.1–19.5 vs <9.5%	3.65	2.87, 4.65	<.001			
Proteinuria	Present	1.01	0.76, 1.33	0.97			
Retinopathy severity	21 vs 10	1.01	0.80, 1.27	0.94			
	31–37 vs 10	1.20	0.95, 1.51	0.13			
	43–53 vs 10	1.11	0.83, 1.48	0.48			
15-level retinopathy severity	Per 2 steps	1.05	0.99, 1.12	0.12	0.92	0.86, 0.99	0.03
Systolic Blood Pressure	Per 10 mm Hg	1.05	0.99, 1.11	0.14			
Diastolic Blood Pressure	Per 10 mm Hg	1.05	0.97, 1.13	0.22			
Hypertension	Present	1.11	0.86, 1.44	0.42			
Smoking History	Past vs never	0.98	0.74, 1.29	0.88			
	Current vs never	1.23	0.99, 1.54	0.07			
Education	Per 4 years	0.98	0.90, 1.06	0.62			
Body mass index	Per 4 kg/m^2	1.08	1.00, 1.17	0.04	1.16	1.07, 1.26	<.001

Abbreviations: HR=hazard ratio; CI=confidence interval

*All variables included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.

Table 4

Associations with Incident Proliferative Diabetic Retinopathy.

		Univariate			Multivariate*		
Risk variable	**Level**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Sex	Male	1.02	0.81, 1.28	0.89			
Age at diagnosis	10–19 yrs vs <10 yrs	0.94	0.72, 1.23	0.67			
	20–29 yrs vs <10 yrs	0.94	0.69, 1.28	0.67			
Glycosylated hemoglobin A_1	Per 1%	1.37	1.30, 1.45	<.001	1.38	1.31, 1.46	<.001
Glycosylated hemoglobin A_1 quartiles	9.5–10.5 vs <9.5%	2.91	1.89, 4.48	<.001			
	10.6–12.0 vs <9.5%	4.08	2.73, 6.10	<.001			
	12.1–19.5 vs <9.5%	6.29	4.23, 9.33	<.001			
Proteinuria	Present	2.12	1.53, 2.92	<.001	1.83	1.31, 2.56	<.001
Retinopathy severity	21 vs 10	1.84	1.27, 2.67	0.001			
	31–37 vs 10	4.19	3.03, 5.80	<.001			
	43–53 vs 10	6.75	4.66, 9.76	<.001			
15–level retinopathy severity	Per 2 steps	1.56	1.45, 1.68	<.001			
Systolic Blood Pressure	Per 10 mmHg	1.21	1.12, 1.32	<.001	1.14	1.04, 1.25	.005
Diastolic Blood Pressure	Per 10 mmHg	1.30	1.16, 1.46	<.001			
Hypertension	Present	1.73	1.25, 2.40	<.001			
Smoking History	Past vs never	0.91	0.61, 1.35	0.63			
	Current vs never	1.22	0.91, 1.63	0.18			
Education	Per 4 years	1.05	0.94, 1.19	0.38			
Body mass index	Per 4 kg/m^2	1.17	1.05, 1.30	0.004	1.21	1.07, 1.36	0.002

Abbreviations: HR=hazard ratio; CI=confidence interval

*All variables included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.

Table 5

Associations with 2-Step Improvement In Diabetic Retinopathy.

		Univariate			Multivariate*		
Risk variable	**Level**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Sex	Male	0.60	0.44, 0.83	0.002	0.55	0.40, 0.77	<.001
Age at diagnosis	10–19 yrs vs <10 yrs	1.37	0.95, 1.98	0.09			
	20–29 yrs vs <10 yrs	0.97	0.62, 1.51	0.88			
Glycosylated hemoglobin A_1	Per 1%	0.86	0.79, 0.94	<.001	0.84	0.77, 0.91	<.001
Glycosylated hemoglobin A_1 quartiles	9.5–10.5 vs <9.5%	0.70	0.46, 1.06	0.09			
	10.6–12.0 vs <9.5%	0.53	0.35, 0.82	0.004			
	12.1–19.5 vs <9.5%	0.45	0.28, 0.72	<.001			
Proteinuria	Present	0.61	0.34, 1.11	0.11			
Retinopathy severity	21 vs 10	1.06	0.67, 1.68	0.81			
	31–37 vs 10	1.08	0.70, 1.66	0.74			
	43–53 vs 10	1.39	0.84, 2.29	0.20			
15-level retinopathy severity	Per 2 steps	1.07	0.96, 1.19	0.20	1.10	0.99, 1.23	0.09
Systolic Blood Pressure	Per 10 mm Hg	1.02	0.92, 1.14	0.71			
Diastolic Blood Pressure	Per 10 mm Hg	1.03	0.88, 1.19	0.73			
Hypertension	Present	1.22	0.78, 1.90	0.38			
Smoking History	Past vs never	1.04	0.67, 1.62	0.87			
	Current vs never	0.64	0.42, 0.97	0.04			
Education	Per 4 years	1.20	0.99, 1.46	0.06			
Body mass index	Per 4 kg/m^2	1.06	0.91, 1.24	0.45			

Abbreviations: HR=hazard ratio; CI=confidence interval

*All variables included in a single model. Missing rows indicate that variable was not significant and thus not included in the final multivariate model.