Risk Factors for the Development of Retinopathy in Prediabetes and Type 2 Diabetes: The Diabetes Prevention Program Experience

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OBJECTIVE

To determine glycemic and nonglycemic risk factors that contribute to the presence of diabetic retinopathy (DR) before and after the onset of type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

During the Diabetes Prevention Program (DPP) and DPP Outcome Study (DPPOS), we performed fundus photography over time in adults at high risk for developing T2D, including after they developed diabetes. Fundus photographs were graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system, with DR defined as typical lesions of DR (microaneurysms, exudates, hemorrhage, or worse) in either eye.

RESULTS

By DPPOS year 16 (∼20 years after random assignment into DPP), 24% of 1,614 participants who had developed T2D and 14% of 885 who remained without diabetes had DR. In univariate analyses, using results from across the entire duration of follow-up, American Indian race was associated with less frequent DR compared with non-Hispanic White (NHW) race, and higher HbA_{1c}, fasting and 2-h plasma glucose levels during an oral glucose tolerance test, weight, and history of hypertension, dyslipidemia, and smoking, but not treatment group assignment, were associated with more frequent DR. On multivariate analysis, American Indian race was associated with less DR compared with NHW (odds ratio [OR] 0.36, 95% CI 0.20–0.66), and average HbA_{1c} was associated with more DR (OR 1.92, 95% CI 1.46–1.74 per SD [0.7%] increase in HbA_{1c}).

CONCLUSIONS

DR may occur in adults with prediabetes and early in the course of T2D. HbA_{1c} was an important risk factor for the development of DR across the entire glycemic range from prediabetes to T2D.

Microvascular lesions of the retina constitute a classical diabetes-related complication (diabetic retinopathy [DR]), and such lesions herald progressive retinal disease that can result in vision loss. The strong association of hyperglycemia with retinopathy has been firmly established in type 1 diabetes, where improving glycemic control has a major impact on reducing the development and slowing the progression of retinopathy (1). Similar data have been generated in type 2 diabetes (T2D)

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*A complete list of the DPPOS Study Group can be found in the supplementary material online.

PATHOPHYSIOLOGY/COMPLICATIONS

(2–4). Our initial results from the Diabetes Prevention Program (DPP) suggested that lesions consistent with DR were present in 12.6% of participants who had progressed to diabetes, on the basis of an oral glucose tolerance test (OGTT), and in 7.9% among a subgroup of participants who had not progressed to diabetes at the time of evaluation (5).

We have now examined the prevalence and severity of DR by fundus photography in the entire cohort, regardless of diabetes status, over 20 years of follow-up to determine whether and to what extent retinopathy occurs before the onset of diabetes and among adults with T2D of known duration. In addition, we determined the degree to which glycemia (from across the prediabetic through the diabetic range) and nonglycemic risk factors contribute to the presence of retinopathy. We report the prevalence, not the incidence, because we did not determine retinopathy status at the beginning of the DPP study and because the cohorts evaluated for retinopathy at the four time points are not constant.

RESEARCH DESIGN AND METHODS

The design, implementation, and primary results of the DPP have been previously reported (6,7). In brief, the DPP was a National Institutes of Health–sponsored, three-arm, randomized, placebo (PLB)-controlled trial to determine whether metformin (MET) or an intensive lifestyle (ILS) intervention aimed at weight loss would reduce the prevalence of diabetes in adults at high risk for developing diabetes. High risk was defined as having impaired glucose tolerance (IGT) (prediabetes) plus elevated fasting glucose and a BMI $\geq$24 kg/m^2 ($>$22 kg/m^2 in Asian patients). Participants were randomly assigned to the PLB group, MET group, or ILS group. The primary results of the DPP study have been reported (7). The DPP Outcomes Study (DPPOS) is a long-term longitudinal, observational follow-up of the DPP cohort. The DPPOS has subsequently followed these participants for an additional 19 years until 2020. During both DPP and DPPOS, diabetes was diagnosed using American Diabetes Association criteria based on a 2 h OGTT done annually, a fasting glucose measured at 6 months between OGTTs, or, more recently, an annual HbA_{1c} measurement $\geq$6.5% confirmed with glucose-based testing. Of note, testing of glycemia has been performed routinely and consistently during DPP and DPPOS; therefore, the onset of diabetes has been determined precisely within a 6 month period. During DPPOS, four sets of stereoscopic fundus photographs were taken: one in a subset of participants at the beginning of DPPOS (mean 5.6 years [range 3.9–7.6 years] after random assignment into DPP) and again in the entire available cohort at DPPOS years 5, 11, and 16.

At the first DPPOS study visit (mean 4.2 years [range 0.0–6.3 years] after random assignment), available participants who had progressed to diabetes (594 [68%] of 876) and a subset of those who had not progressed (302 [16%] of 1,832) underwent seven-field stereo fundus photography, as previously described (5). Fundus photography was again performed in all available and consenting participants at DPPOS years 5, 11, and 16 (mean time since random assignment 9.1 [range 7.3–11.8] years, 14.5 [12.9–16.7] years, and 20.0 [18.3–22.1] years, respectively). All fundus photographs were graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system (8) by the Wisconsin Reading Center at the University of Wisconsin. DR was diagnosed by the presence of typical lesions generally believed to be consistent with DR (microaneurysms, exudates, or hemorrhage) in either eye (ETDRS score $\geq$20 in either or both eyes).

Weight, height, BMI, blood pressure (BP), HbA_{1c}, fasting glucose, 2-h glucose (for those who had not yet developed diabetes), fasting lipid profile (total, HDL, and calculated LDL cholesterol and triglycerides), urinary albumin-to-creatinine ratio, and estimated glomerular filtration rate (based on serum creatinine as estimated using the Chronic Kidney Disease Epidemiology Collaboration equation) (9) were determined annually during DPP and DPPOS. Hypertension and dyslipidemia were defined using criteria in effect at the start of the DPP, that is, a BP $>$140/90 or use of antihypertension medications and an LDL cholesterol $>$130 mg/dL, HDL cholesterol $<$40 mg/dL, triglycerides $>$200 mg/dL, or use of lipid-lowering medications. Smoking history, pregnancy history, and history of gestational diabetes mellitus were also obtained at DPP baseline. Insulin sensitivity (1 / fasting insulin and HOMA of insulin resistance [HOMA-IR]) and insulin secretion (HOMA-B and insulinogenic index [($\Delta Ins_{120} - Ins_0$) / ($Glu_{u120} - Glu_0$)]) were determined annually on the basis of the glucose and insulin levels measured during OGTTs, and the oral disposition index (presumably a measure of insulin secretion relative to insulin sensitivity) was calculated (1 / fasting insulin × [$\Delta Ins_{120} - Ins_0$] / [$Glu_{u120} - Glu_0$]). The potential risk factors considered were the demographic variables and the DPP baseline and average values over time of weight, fasting glucose, 2 h glucose, HbA_{1c}, systolic BP (SBP) and diastolic BP (DBP) up to and including the time points at which each set of stereoscopic fundus photographs were taken.

Statistical Analysis

Complete case analyses using all available data were used. There were no missing baseline values for the risk factors (Table 1). Average values over time were calculated using all available data. Prevalence estimates of retinopathy across the different sex, race/ethnicity, and treatment groups were compared using Pearson χ^2 test of independence. Mean values of age and BMI at baseline were compared between those with and without retinopathy using two-sample *t* tests. The relationships between the prevalence of retinopathy and the average fasting glucose or HbA_{1c} during follow-up were estimated using a generalized additive model with a logit link, which assumes a piecewise polynomial function with degree 4 and 3 evenly spaced knots. Finally, generalized estimating equations were used to model the four repeated measures of retinopathy with a logit link and unstructured correlation structure. Univariate and multivariate generalized estimating equation models, whose covariates are selected using a stepwise variable selection procedure with *P* value thresholds of 0.05 and variance inflation factor thresholds of 3 (Table 2), were fitted respectively to assess the marginal impacts of candidate risk factors and the conditional effects of selected prognostic factors with strong effects on retinopathy risks. Sensitivity analyses stratified by age categories ($\leq$45, 45–59, $\geq$60 years) were performed to examine heterogeneity in different age-groups. All calculations were done using SAS 9.4 software.

Table 1—Characteristics of participants with prediabetes and T2D by retinopathy status at DPPOS year 16

Characteristic	No diabetes (*n* = 747)			T2D (*n* = 1,546)		
	With retinopathy	Without retinopathy	*P*	With retinopathy	Without retinopathy	*P*
Participants, *n*	110 (15)	637 (85)		372 (24)	1,174 (76)	
Sex			0.8500			0.0928
Male	32 (29.1)	191 (30.0)		136 (36.6)	374 (31.9)	
Female	78 (70.9)	446 (70.0)		236 (63.4)	800 (68.1)	
Race/ethnicity			0.3827			0.0217
NHW	60 (54.5)	364 (57.1)		191 (51.3)	580 (49.4)	
African American	23 (20.9)	104 (16.3)		92 (24.7)	261 (22.2)	
Hispanic	15 (13.6)	102 (16.0)		62 (16.7)	184 (15.7)	
Asian	7 (6.4)	23 (3.6)		17 (4.6)	62 (5.3)	
American Indian	5 (4.5)	44 (6.9)		10 (2.7)	87 (7.4)	
DPP treatment group			0.4058			0.8359
ILS	38 (34.5)	247 (38.8)		111 (29.8)	359 (30.6)	
MET	42 (38.2)	202 (31.7)		119 (32.0)	387 (33.0)	
PLB	30 (27.3)	188 (29.5)		142 (38.2)	428 (36.5)	
Ever smoking at baseline	41 (37)	247 (39)	0.7199	146 (39)	492 (42)	0.1347
Gestational diabetes mellitus at baseline (female subjects only)	7 of 78 (9.0)	45 of 446 (10.1)	0.7612	43 of 235 (18.3)	153 of 800 (19.1)	0.7760
Ever pregnant at baseline (female subjects only)	65 of 78 (83.3)	378 of 446 (84.8)	0.7489	203 of 236 (86.0)	689 of 800 (86.1)	0.9664
Age at random assignment (year)	52.42 (10.49)	53.01 (10.29)	0.6544	49.64 (9.76)	49.84 (9.79)	0.7074
Up to last fundus examination						
HbA_{1c} (%)	5.70 (0.33)	5.65 (0.33)	0.1992	6.61 (1.02)	6.21 (0.65)	<0.0001
Fasting glucose (mg/dL)	101.8 (5.26)	101.7 (5.80)	0.9859	129.6 (25.56)	118.8 (15.71)	<0.0001
120-min glucose (mg/dL)	139.8 (20.98)	139.5 (18.84)	0.9554	180.3 (28.90)	175.7 (25.47)	0.0090
Weight (kg)	88.29 (17.83)	87.07 (17.32)	0.5575	95.54 (21.58)	93.31 (19.97)	0.1398
SBP (mmHg)	122.6 (8.71)	120.6 (10.21)	0.0179	123.3 (9.76)	121.9 (9.46)	0.0233
DBP (mmHg)	74.32 (6.07)	72.96 (6.23)	0.0852	75.17 (6.77)	74.25 (6.21)	0.0440
Baseline						
HbA_{1c} (%)	5.85 (0.45)	5.83 (0.44)	0.6870	6.02 (0.55)	5.97 (0.51)	0.0759
Weight (kg)	91.81 (19.13)	90.77 (18.45)	0.6517	96.27 (21.64)	94.23 (19.65)	0.2166
SBP (mmHg)	123.1 (13.27)	122.9 (14.81)	0.6768	124.7 (15.50)	123.4 (14.59)	0.3564
DBP (mmHg)	77.54 (8.91)	77.56 (9.11)	0.8408	79.21 (9.68)	78.26 (9.51)	0.2214
BMI (kg/m^2)	33.19 (5.92)	32.79 (6.25)	0.3453	34.58 (6.92)	34.07 (6.38)	0.2811
Adiponectin (μg/mL)	8.49 (3.27)	8.85 (3.67)	0.4948	7.61 (3.39)	7.48 (3.35)	0.5108
Fasting glucose (mg/dL)	103.3 (6.33)	103.3 (6.69)	0.9578	109.4 (8.94)	108.0 (8.77)	0.0115
120-min glucose (mg/dL)	159.9 (16.36)	159.0 (15.50)	0.7613	168.4 (17.46)	167.9 (17.15)	0.6223
HOMA-B*	195.6 (135.4–254.3)	193.0 (135.3–276.1)	0.7186	201.7 (134.7–286.2)	211.0 (144.4–285.7)	0.1700
HOMA-IR	5.32 (3.70–7.44)	5.45 (3.63–7.62)	0.6634	6.80 (4.45–9.64)	6.73 (4.61–9.50)	0.8601
Insulinogenic index (μU/mg)	124.2 (81.85–183.4)	113.8 (75.00–174.6)	0.3285	94.20 (63.20–135.2)	100.0 (63.80–150.0)	0.1307
Oral disposition index	2,299 (1,308–5,008)	2,353 (1,154–4,853)	0.5941	2,238 (1,151–4,371)	2,443 (1,199–4,812)	0.2410
Albumin-to-creatinine ratio (mg/g)	5.47 (3.65–9.75)	5.22 (3.52–9.02)	0.5917	6.31 (4.15–12.10)	5.43 (3.80–9.21)	0.0009
hs-CRP (mg/dL)	0.38 (0.13–0.70)	0.34 (0.15–0.67)	0.7966	0.40 (0.21–0.81)	0.37 (0.17–0.76)	0.0469
HDL-C (mg/dL)	48.06 (14.01)	47.97 (12.10)	0.5186	42.00 (35.00–50.00)	43.00 (37.00–51.00)	0.0237
Total cholesterol (mg/dL)	202.1 (36.27)	204.1 (36.67)	0.6865	202.5 (33.09)	203.4 (35.35)	0.6454
LDL-C (mg/dL)	123.6 (31.27)	125.2 (33.15)	0.7294	124.8 (30.55)	124.6 (32.88)	0.8750
Triglycerides (mg/dL)	125.0 (95.00–189.0)	136.0 (97.00–190.0)	0.5830	142.0 (103.0–200.0)	148.0 (102.5–206.0)	0.6206
Duration of T2D up to the last fundus examination (years)	0.00 (0.00)	0.00 (0.00)	—	12.52 (5.43)	10.44 (5.72)	<0.0001

Data are *n* (%) for categorical variables, mean (SD) for continuous variables, and median (interquartile range) for skewed continuous variables. *P* values are from Pearson χ^2 test or ANOVA comparing the four groups of participants. HDL-C, HDL cholesterol; LDL-C, LDL cholesterol.

RESULTS

Participants

Of the 3,234 participants randomly assigned in the DPP, 2,779 were enrolled in DPPOS. A total of 899 participants (34% of those who completed the year 1 visit) had retinal photography performed at the first DPPOS visit (referred to as year 1); this represented 594 of those who had developed T2D (68%) and a subset of 302 who had not developed T2D (16%) (see *Research Design and Methods*). At years 5, 11, and 16, 2,128 (84%), 2,086 (92%), and 1,563 (76%) participants, respectively, underwent retinal photography. The DPP baseline characteristics of the participants with T2D and without T2D with and

Table 2—ORs and 95% CIs associated with a 1-SD change in continuous risk factors or compared with the reference group for categorical risk factors for DR at DPPOS years 1, 5, 11, and 16

Factor	SD of factor	OR (95% CI)	*P*
Age at randomization (years)	10.7	0.95 (0.85–1.06)	0.363
Female sex		0.82 (0.67–1.01)	0.061
Race/ethnicity			
African American vs. NHW		1.27 (0.99–1.63)	0.056
Hispanic vs. NHW		0.95 (0.72–1.25)	0.699
Asian vs. NHW		0.99 (0.63–1.55)	0.963
American Indian vs. NHW		**0.44 (0.25–0.79)**	**0.005**
Progressed to T2D		**1.47 (1.22–1.79)**	**<0.0001**
Average HbA_{1c}* (%)	**0.7**	**1.59 (1.46–1.74)**	**<0.0001**
Average fasting glucose* (mg/dL)	**18.0**	**1.61 (1.48–1.75)**	**<0.0001**
Average 2-h glucose* (mg/dL)	**29.8**	**1.17 (1.07–1.27)**	**0.001**
Weight (kg)	**19.6**	**1.13 (1.03–1.25)**	**0.015**
Average SBP* (mmHg)	**9.7**	**1.19 (1.09–1.31)**	**<0.0001**
Average DBP* (mmHg)	**6.3**	**1.18 (1.06–1.31)**	**0.002**
Average albumin-to-creatinine ratio (mg/mL)	**51.5**	**1.09 (1.01–1.17)**	**0.019**
Baseline adiponectin (μg/mL)	3.5	0.99 (0.11–1.11)	0.872
Baseline CRP (mg/dL)	**0.7**	**1.08 (1.00–1.17)**	**0.049**
Hypertension history**		**1.36 (1.07–1.74)**	**0.013**
Dyslipidemia history**		**1.34 (1.06–1.69)**	**0.013**
Current smoking**		**1.53 (1.05–2.22)**	**0.027**

Univariate logistic regression adjusted for the risk factor only. Boldface indicates significance at $P < 0.05$ in the univariate model. *Average during DPP/DPPOS follow-up up to the time of retinopathy measurement (DPPOS years 1, 5, 11, and 16) because all four retinopathy measurements were used as outcomes in a generalized mixed model. **Reference group was no hypertension, no dyslipidemia, or nonsmoker.

without retinopathy are shown in Table 1. The baseline characteristics of those who underwent fundus photography were similar at each time point and are shown in Supplementary Table 1. It should be noted that among those who underwent fundus photography at DPPOS years 5, 11, and 16, the percentage with T2D was similar (67.5%, 69.1%, and 71.8%, respectively).

Prevalence of DR in Participants With Diabetes Versus Those Without Diabetes

At DPPOS year 16, 385 (24%) of the 1,614 participants who had developed diabetes had retinopathy, and 127 (14%) of the 885 without diabetes had developed retinopathy; this difference was significant at $P < 0.001$. There was no difference in sex, or SBP or DBP at baseline between participants with and those without T2D or between those with or without retinopathy. Participants with T2D were more likely to be African American and tended to be younger and have a higher BMI at baseline, although these difference in age and BMI were not significant. Not unexpectedly, and consistent with the overall results of DPP and DPPOS, the prevalence of T2D was higher (69%) in the PLB group than in either the MET (63%) or ILS (62%) groups.

Glycemic and Nonglycemic Risk Factors for the Development of Retinopathy

Glycemic and nonglycemic risk factors for the presence of retinopathy are summarized in Table 2. Combining the participants with T2D and prediabetes and over all examinations, retinopathy was less common in American Indian participants (odds ratio [OR] 0.44, 95% CI 0.25–0.79, $P = 0.005$ vs. non-Hispanic White [NHW] participants). Although slightly less common in female participants (OR 0.82, 95% CI 0.69–1.01, $P = 0.061$) and more common in African American participants (OR 1.27, 95% CI 0.99–1.63, $P = 0.056$), these latter findings were not statistically significant. Using univariate logistic regressions adjusted for one covariate of interest per model, retinopathy was associated with diabetes status (OR 1.47, 95% CI 1.22–1.79, $P < 0.001$ vs. no diabetes), duration of diabetes at the time of fundus examination (OR 1.30, 95% CI 1.18–1.44, $P < 0.001$ per SD), and higher average HbA_{1c} (OR 1.59, 95% CI 1.46–1.74, $P < 0.001$ per SD), fasting plasma glucose (OR 1.61, 95% CI 1.48–1.75, $P < 0.001$ per SD), and 2-h plasma glucose (OR 1.17, 95% CI 1.07–1.27, $P = 0.001$ per SD) during DPP/DPPOS follow-up until the time of the fundus examination (Table 2). Of note, the OR values for the continuous covariates correspond to a 1-SD change in the covariate; these values are listed in Table 2.

Nonglycemic risk factors for retinopathy included a history of hypertension (OR 1.36, 95% CI 1.07–1.74, $P = 0.013$), history of dyslipidemia (OR 1.34, 95% CI 1.06–1.69, $P = 0.013$), higher mean SBP (OR 1.19, 95% CI 1.09–1.31, $P < 0.001$ per SD) and DBP (OR 1.18, 95% CI 1.06–1.31, $P = 0.002$ per SD), weight (OR 1.13, 95% CI 1.03–1.25, $P = 0.015$ per SD) during DPP/DPPOS follow-up, and current, but not previous, smoking history (OR 1.53, 95% CI 1.05–2.22, $P = 0.027$). Other nonglycemic risk factors that were not associated with the presence of retinopathy at year 16 included history of pregnancy, history of gestational diabetes mellitus, hs-CRP or adiponectin at baseline, measures of insulin resistance (1 / fasting insulin, HOMA-IR) or insulin secretion (HOMA-B, insulinogenic index) and urine albumin-to-creatinine ratio.

In a multivariate regression model (Table 3), mean HbA_{1c} during follow-up remained significantly associated (OR 1.65, 95% CI 1.48–1.83, $P < 0.0001$ per SD [0.7%]), and baseline adiponectin concentration was positively associated ($P = 0.04$) with the prevalence of retinopathy at year 16. American Indian participants were still less likely to have retinopathy than NHW participants (OR 0.36, 95% CI 0.20–0.66, $P = 0.001$). The OR for African American participants remained nonsignificant but was nominally lower than

Table 3—Multivariate regression model assessment of risk factors for DR at DPPOS year 16

Intercept	OR	95% CI	OR per unit	*P*
African American	0.93	0.70–1.24	vs. NHW	0.638
Hispanic	0.75	0.55–1.01	vs. NHW	0.062
Asian	0.84	0.52–1.36	vs. NHW	0.482
American Indian	**0.36**	**0.20–0.66**	vs. NHW	**0.001**
Female sex	0.80	0.62–1.03	vs. male	0.083
ILS	1.10	0.86–1.41	vs. PLB	0.459
MET	1.19	0.94–1.52	vs. PLB	0.152
Age at random assignment (years)	0.94	0.82–1.09	per 10.68§	0.426
Duration of T2D (years)	1.03	0.92–1.17	per 6.96§	0.574
Average HbA_{1c} in follow-up* (%)	**1.65**	**1.48–1.83**	**per 0.71§**	**<0.0001**
Average weight in follow-up* (kg)	0.95	0.84–1.06	per 19.62§	0.344
Average DBP in follow-up* (mmHg)	6.33	0.98–1.23	per 6.33§	0.110
Adiponectin at baseline (mg/dL)	1.13	1.00–1.28	per 3.47§	0.044

Multivariate logistic regression adjusted for age, sex, race/ethnicity, treatment assignment, and the presence of diagnosed diabetes. Boldface indicates significance at $P < 0.05$ in the multivariate model. *Average during DPP/DPPOS follow-up (before onset of retinopathy). §1 SD.

for NHW participants rather than higher (OR 0.93, 95% CI 0.70–1.24, $P = 0.64$), and females still tended to be less likely than males to develop retinopathy (OR 0.80, 95% CI 0.62–1.03, $P = 0.08$), although these did not reach statistical significance in the multivariate model. We repeated the multivariate regression analysis in Table 3 in a sensitivity analysis when samples were restricted to participants free of diabetes by DPPOS year 16 (results not shown), and none of the candidate risk factors were associated with retinopathy in this subgroup analysis.

The risk of retinopathy increased across the continuum of glycemia from normal glucose regulation to prediabetes (impaired fasting glucose, IGT) to diabetes. Combining participants with and without diabetes, Figure 1 shows a progressively increasing risk of retinopathy with higher HbA_{1c} and plasma glucose levels. For fasting plasma glucose (Fig. 1*A*), the prevalence of retinopathy began to increase (slope 0.021 ± 0.007, $P = 0.0025$) at plasma glucose levels below those diagnostic for diabetes (<100 mg/dL), although the slope appeared to increase (0.037 ± 0.006, $P < 0.0001$, P between slopes = 0.0802) when plasma glucose reached the level considered diagnostic of diabetes (≥126 mg/dL). A similar relationship was seen for HbA_{1c} (Fig. 1*B*). The risk of retinopathy appeared to increase across the entire range of HbA_{1c} values, even into the range not currently considered diagnostic of diabetes (<6.5%, slope 0.36 ± 0.16, $P = 0.0257$) and again appeared to increase (slope 0.72 ± 0.14, $P < 0.0001$, P between slopes = 0.0928) after the HbA_{1c} reached the diagnostic value of 6.5%. There were no differences by race/ethnicity in the threshold for retinopathy by fasting glucose or HbA_{1c} (data not shown). After stratifying the participants into those who remained diabetes free at the end of follow-up and those who developed diabetes before DPPOS year 16, the relationship between fasting glucose and DR was present in the cohort with diabetes (Fig. 1*A*) but disappeared in the cohort that remained free of diabetes (Fig. 1*A*). While examining the relationships between retinopathy risks and average SBP and DBP during follow-up (Supplementary Fig. 1), retinopathy risks increased with average DBP levels but peaked around an average SBP of 145 mmHg.

Progression and Regression of Retinopathy During DPPOS

Progression of retinopathy was defined as a three-step progression between successive time points (for those who had fundus photography at two successive time points) on the ETDRS grading system using both eyes, similar to what was done in Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) (10) and over the entire course of the follow-up (for those who had fundus photography at both years 1 and 16). Three-step progression of retinopathy between examinations was low, occurring in 0.9%, 0.7%, and 2.5% between years 1 and 5, years 5 and 11, and years 11 and 16, respectively. Over time, the frequency of three-step progression in those who had not developed diabetes was low and unchanged (0.99%, 1.41%, and 0.95% between years 1 and 5, years 5 and 11, and years 11 and 16, respectively). In those who did develop diabetes, the frequency of three-step progression, albeit low, did increase ($P = 0.002$) over time (0.91%, 2.36%, and 3.45% between years 1 and 5, years 5 and 11, and years 11 and 16, respectively). Over the entire study duration (DPPOS years 1–16), three-step progression occurred in 2.27% of participants who had not developed diabetes and in 4.64% of those who developed diabetes ($P = 0.0075$). A one-step or greater regression to a lower ETDRS score occurred in 8.12%, 6.55%, and 7.89% of participants between years 1 and 5, years 5 and 11, and years 11 and 16, respectively.

Macular Edema

Clinically significant macular edema based on fundus photography was present overall in few participants, with <0.5% having it over the entire course of follow-up.

CONCLUSIONS

We believe that this study is the largest prospective, long-term, longitudinal follow-up with retinal photography of a cohort of adults at increased risk for the development of T2D and a well-defined onset of diabetes. We were able to evaluate the prevalence of retinopathy in 2,086 participants over 11 years and 1,553 over 16 years after completion of their participation in the DPP. All participants had prediabetes (elevated fasting glucose and IGT) and a BMI ≥24 kg/m^2 at the time of enrollment in DPP. The time to onset of diabetes, by American Diabetes Association criteria (based on a 2h OGTT done annually, a fasting glucose done at 6 months between OGTTs, or, more recently, an

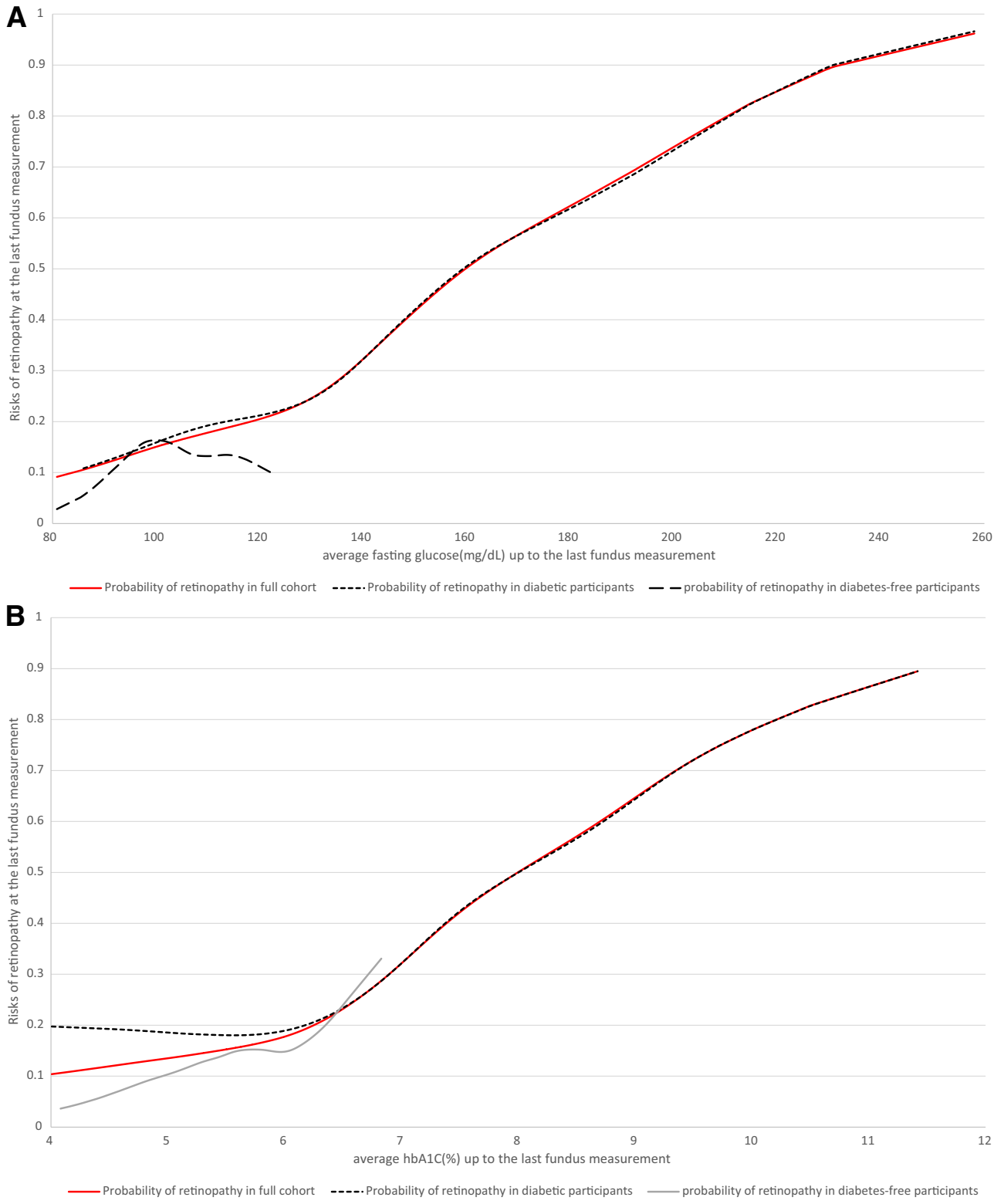

Figure 1—Prevalence of retinopathy at DPPOS year 16 by average fasting plasma glucose (*A*) and HbA_{1c} (*B*) in the overall cohort, participants with diabetes, and participants without diabetes up to the end of follow-up.

HbA_{1c} ≥6.5% confirmed with glucose-based testing), was known in participants within a 6 month time window. This enabled the determination of the presence of DR in prediabetes and from the time of biochemical onset of T2D rather than from the time of clinical diagnosis, as in most studies. We have previously published (5) that in a subset of DPP participants, 12.6% of those who had developed diabetes with a mean duration of 3.1 years and 7.9% of those who had not yet developed diabetes had retinopathy.

Our current data show that at 5, 11, and 16 years after the conclusion of

DPP, 12.0%, 14.4%, and 12.5%, respectively, of participants who had fundus photographs and had developed diabetes, and 7.7%, 8.7%, and 5.0%, respectively, of those who had fundus photographs and had not yet developed diabetes had DR. Colagiuri et al. (12), in a review of nine articles including 41,411 subjects, showed that the fasting plasma glucose threshold for the appearance of DR is 6.4 mmol/L (117 mg/dL), slightly lower than the level for diagnosis of diabetes. Our data support those of Colagiuri et al., with the prevalence of retinopathy appearing to increase at fasting plasma glucose and HbA_{1c} values that are below the cutoff currently considered diagnostic of diabetes (126 mg/dL and 6.5%, respectively). However, below an HbA_{1c} of 6.4%, our data demonstrate a continuous increase in prevalence of DR through the entire range of HbA_{1c}, albeit with a shallower trajectory than that observed at HbA_{1c} of $\geq$6.5%. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (13–15), 50–52% of ~3,000 enrolled subjects with an average age of 61 years and an average diabetes duration of ~10 years had retinopathy. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study (16,17), 40% of 3,204 subjects with a mean age of 66 years had retinopathy after a mean duration of 6–7 years. Nagi et al. (18) found that DR was present in 37.8% of a Pima Indian cohort with diabetes and in 5.2% of subjects without diabetes. In this cohort, DR was present in 11.2% of subjects at the time of diagnosis, 8.3% of recently diagnosed subjects who had had a nondiabetic OGTT within the past 4 years, and 12% of those with IGT. Thus, there appears to be a lower prevalence of DR in Pima Indians than in the cohorts from the ACCORD and ADVANCE studies; however, this conclusion must be tempered because the ascertainment of diabetes onset was different in the Pima Indian studies than in the ACCORD and ADVANCE studies. In our data, American Indian participants were less likely than NHW participants (OR 0.36, 95% CI 0.20–0.66, P = 0.001) to develop retinopathy by 16 years after DPP. Overall, the substantially lower frequency of DR in the DPPOS diabetes cohort at a mean diabetes duration of 6.8 (SD 7.0) years (median 4.9 years, interquartile range 0.0–13.0 years) at the time of the final set of fundus photographs (compared with the studies cited above) strongly supports a longer actual duration of hyperglycemia in studies that rely on clinical diagnoses.

Our data for prediabetes are similar to those reported in a number of cross-sectional studies with a prevalence of retinopathy in prediabetic participants ranging from 8.2 to 20.9%. In the Gutenberg Health Study, Lamparter et al. (19) found that 1,112 (22.3%) of the 4,972 participants had prediabetes on the basis of an HbA_{1c} of 5.7–6.4%. Of those with prediabetes, 8.2% had retinopathy. Chen et al. (20) compared 23 subjects with prediabetes with 23 matched control subjects. DR was present in 20.9% of the subjects with prediabetes compared with none of the control subjects. The NEPI Antidiabetes Study (NANSY-Eye) from Sweden reported that 10.4% of 154 subjects with prediabetes (fasting plasma glucose 100–110 mg/dL) had retinopathy (21), and Nagi et al. (18) found that 12% of Pima Indian subjects with IGT had retinopathy. Perreault et al. (22) showed that in the DPP/DPPOS cohort, regression to normal glucose regulation at any time during the DPP clinical trial resulted in a 56% reduction in the prevalence of diabetes at 10 years and a reduced OR of 0.765 (95% CI 0.635–0.922, P = 0.005) for an aggregate microvascular outcome and 0.675 (95% CI 0.505–0.898, P = 0.007) for the prevalence of retinopathy.

The risk of retinopathy was lower in American Indian participants in our study. Although in univariate analyses the risk of retinopathy was borderline greater in African American participants, this difference was not present after multivariate analysis adjusting for average HbA_{1c}, weight, and DBP during follow-up, suggesting that other factors associated with race, such as hypertension, may have accounted for these differences. In univariate analyses, retinopathy was associated with measures of glycemia (HbA_{1c}, fasting plasma glucose, 2 h plasma glucose), increased weight, and higher BP (SBP, DBP, presence of hypertension) during the DPP/DPPOS follow-up. Although there was a tendency for greater risk in males than females and in current smokers, this association was not present on multivariate analysis. There was no association between the presence of retinopathy at year 16 and a history of pregnancy or gestational diabetes mellitus or adiponectin, measures of insulin resistance or insulin secretion, or the urine albumin-to-creatinine ratio. After multivariate regression analysis, the only risk factors remaining were a strong association of retinopathy with HbA_{1c} and a reduced risk in American Indian participants. Previous cross-sectional studies in T2D have shown an association of retinopathy with various measures of glycemia, most notably HbA_{1c}. Although studies in prediabetes (18–21) have not shown an association between HbA_{1c} and retinopathy in the prediabetes range, changes in retinal physiology in adults with prediabetes have been shown to correlate with glycemia. De Clerck et al. (23) for the Maastrict Study and Yazgan et al. (24) found that thinning of the retina, as measured by optical coherence tomography, in subjects with prediabetes was associated with HbA_{1c}, fasting plasma glucose, and 2-h plasma glucose in the prediabetic range (23,24) and with BMI (24).

Our data (Fig. 1*B*) show a slight increase in the 16-year prevalence of retinopathy based on glycemia in the prediabetic range (HbA_{1c} 5.7–6.5%, fasting plasma glucose 100–125 mg/dL), albeit small compared with the sharp increase that occurred once a diabetic level of glycemia (HbA_{1c} $\geq$6.5%, fasting plasma glucose $\geq$126 mg/dL) was reached. In the Data From an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study, Massin et al. (25) showed in 700 subjects (235 with diabetes, 227 with IGT, and 238 with normal glucose) who were evaluated for retinopathy 10 years after enrollment that 44 had retinopathy. The positive predictive value for retinopathy increased at an HbA_{1c} of 6.0% and a fasting plasma glucose of 108 mg/dL. Gabir et al. (26) found in a Pima Indian cohort that fasting and 2 h postload glucose predicted the appearance of retinopathy at 6.0 mmol/L (108 mg/dL) and 9.0 mmol/L (162 mg/dL), respectively, ranges that indicate impaired fasting glucose and IGT, not diabetes.

In a number of studies, the presence of DR was associated with various inflammatory markers, including CRP (27–32), tumor necrosis factor-α (27,31,32), vascular endothelial growth factor (27), intracellular adhesion molecule (32), soluble gp130 (32), and soluble tumor necrosis factor receptor 1 (32). In our study, the prevalence of retinopathy was associated with hs-CRP (OR 1.08, 95% CI

1.00–1.17, per 1 SD [0.7], P = 0.049) on univariate analysis but not in the multivariate analysis with adjustment for other selected risk factors.

In addition, numerous studies have shown functional abnormalities in the retinas of subjects with prediabetes. Su et al. (33), Sörensen et al. (34) for the Maastrict Study, Lott et al. (35), and Zaleska-Żmijewska et al. (36) found flicker light–induced retinal arteriolar dysfunction in prediabetes. This dysfunction was associated with HbA_{1c} (33,34), fasting plasma glucose (34,35), and 2 h glucose (34).

Our study has some limitations. First, retinopathy was assessed only at four time points separated by ∼5 years, and the populations at each time point were not the same, making comparisons between time points problematic. For example, there were fewer participants available for retinal photography at year 16 (n = 1,563) than at year 11 (n = 2,086); 587 who were evaluated for retinopathy at year 11 were not evaluated at year 16, and 64 who were evaluated at year 16 missed their year 11 measurements. Although comparisons across the time periods should be viewed with care, the risk factor analyses within the time periods are valid. Second, although we determined the onset of diabetes within a 6 month window, we were not able to determine the exact onset of retinopathy other than within 5 year intervals. Third, we do not have an ophthalmologic evaluation at the baseline visit of the DPP. At that time, all participants had prediabetes. Thus, without a baseline assessment, we cannot determine the incidence of retinopathy. Fourth, although there appears to be a lower prevalence of retinopathy at year 16 compared with year 11, there were fewer participants available for retinal photography at year 16 (n = 1,563) than at year 11 (n = 2,086). Moreover, those evaluated at year 11, but not at year 16, had slightly, but significantly, higher SBP (121 vs. 123 mmHg). As shown in Supplementary Table 1, the sample evaluated at year 16 was significantly healthier than the samples at other time points. Conversely, the sample evaluated at year 11 was in worse general health compared with samples at other time points. It is possible that of those evaluated at year 11, but not at year 16, some may have declined examination at year 16 because they had already been diagnosed with DR outside of the study and therefore refused fundus photography at year 16. These differences in the cohorts photographed over time could potentially explain the lower prevalence of retinopathy observed in our cohort at year 16. Finally, in DPP and DPPOS, we were only able to determine associations with glycemia and the many nonglycemic factors noted, but we are not able to assess other factors or metabolites that could contribute to the development of retinopathy since these were not determined. We also cannot address the underlying mechanism by which glycemia contributes to retinopathy or other complications.

In conclusion, in adults at risk for diabetes because of the presence of prediabetes and overweight/obesity, DR begins to develop early during the course of dysglycemia and occurs early in the course of diabetes. There is a lower burden of retinopathy in American Indian patients than NHW patients. Glycemic parameters, most notably HbA_{1c}, appear to be the strongest independent risk factors for DR across the entire span of glycemia, even before the diagnosis of diabetes. Since interventions that reduce the development of diabetes have so far not appeared to reduce the subsequent development of long-term diabetes-related retinopathy, and since such retinopathy is mild and does not threaten vision, screening for retinal changes in persons with prediabetes does not seem to be warranted on the basis of currently available data. Whether interventions to reduce plasma glucose or other metabolic abnormalities during the prediabetes phase will alter the course of long-term complications requires further study.

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