The Effect of Interventions to Prevent Type 2 Diabetes on the Development of Diabetic Retinopathy: The DPP/DPPOS Experience

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OBJECTIVE

To determine whether interventions that slow or prevent the development of type 2 diabetes in those at risk reduce the subsequent prevalence of diabetic retinopathy.

RESEARCH DESIGN AND METHODS

The Diabetes Prevention Program (DPP) randomized subjects at risk for developing type 2 diabetes because of overweight/obesity and dysglycemia to metformin (MET), intensive lifestyle intervention (ILS), or placebo (PLB) to assess the prevention of diabetes. During the DPP and DPP Outcome Study (DPPOS), we performed fundus photography over time on study participants, regardless of their diabetes status. Fundus photographs were graded using the Early Treatment Diabetic Retinopathy Study grading system, with diabetic retinopathy defined as typical lesions of diabetic retinopathy (microaneurysms, exudates, or hemorrhage, or worse) in either eye.

RESULTS

Despite reduced progression to diabetes in the ILS and MET groups compared with PLB, there was no difference in the prevalence of diabetic retinopathy between treatment groups after 1, 5, 11, or 16 years of follow-up. No treatment group differences in retinopathy were found within prespecified subgroups (baseline age, sex, race/ethnicity, baseline BMI). In addition, there was no difference in the prevalence of diabetic retinopathy between those exposed to metformin and those not exposed to metformin, regardless of treatment group assignment.

CONCLUSIONS

Interventions that delay or prevent the onset of type 2 diabetes in overweight/obese subjects with dysglycemia who are at risk for diabetes do not reduce the development of diabetic retinopathy for up to 20 years.

Several randomized clinical trials have shown that the onset of type 2 diabetes (T2D) can be prevented or delayed by intervention before the onset of diabetes (1), including lifestyle (2–5), medication (2,6–9), or surgical (10,11) interventions. It would

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be expected that such interventions would also prevent or delay the development of the micro- and macrovascular and neurological complications of diabetes, but evidence for this is sparse, as reviewed by Nathan et al. (12) We, therefore, evaluated this question with respect to retinopathy in the Diabetes Prevention Program (DPP) and the Diabetes Prevention Program Outcomes Study (DPPOS).

The DPP was a randomized controlled clinical trial of a lifestyle intervention targeting lower weight and increased physical activity or metformin to reduce progression to T2D in a cohort of adults at high risk for development of T2D (prediabetes) (13,14). DPP had a mean follow-up of 3.2 years (range 0.0–5.3 years). The DPPOS has followed these subjects for an additional 19 years as of 2020. Our initial results at DPP-end suggested that lesions consistent with diabetic retinopathy were present in 12.6% of those who had progressed to diabetes, based on oral glucose tolerance testing, and in 7.9% among a subgroup of participants who had not progressed to diabetes at the time of evaluation (14).

We have now examined the prevalence and severity of diabetic retinopathy by fundus photography in the entire cohort over 20 years of follow-up to determine whether the prevalence of diabetic retinopathy differed between treatment groups or use of metformin. We chose to report prevalence not incidence, because we did not have a determination of retinopathy status at the beginning of the DPP study and the cohorts measured 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 (13,14). In brief, the DPP was an National Institutes of Health-sponsored three-arm, randomized, placebo-controlled trial to determine whether, compared with a placebo control group, metformin or an intensive lifestyle intervention aimed at weight loss would reduce the incidence of diabetes in adults at high risk for developing diabetes. High-risk subjects, defined as having impaired glucose tolerance ("prediabetes") plus elevated fasting glucose and BMI $\geq$24 kg/m^2, were randomly assigned to the placebo group (PLB), metformin group (MET), or intensive lifestyle intervention group (ILS). The primary results of the DPP Study have been reported (2). The DPP Outcomes Study (DPPOS) is a long-term longitudinal, observational follow-up of the DPP cohort. During both DPP and DPPOS, diabetes was diagnosed by American Diabetes Association criteria based on a 2-h oral glucose tolerance (OGTT) test done yearly, a fasting glucose done at 6 months between the OGTTs, or, more recently, an HbA_{1c} $\geq$6.5% confirmed with glucose-based testing.

One aim of DPPOS was to determine whether treatment group assignment during DPP had any impact on the subsequent development of microvascular complications. At the study visit at the beginning of DPPOS at a mean of 4.2 years (range 0.0–6.3) postrandomization, available subjects who had progressed to diabetes (n = 595; 68% of 876 who had progressed) and a subset of those who had not progressed (n = 304; 17% of 1,832 who had not progressed) underwent seven-field stereo fundus photography. Fundus photography was again performed on all available and consenting subjects, regardless of diabetes status, at DPPOS years 5, 11, and 16 (mean years since randomization 9.1 [range 7.3–11.8], 14.5 [range 12.9–16.7], and 20.0 [range 18.3–22.1], respectively). All fundus photographs were graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system (15) by the Fundus Photography Reading Center at the University of Wisconsin. Diabetic retinopathy was diagnosed by the presence of typical lesions (microaneurysms, exudates, or hemorrhage) or more advanced lesions in either eye (ETDRS grade of $\geq$20 in either or both eyes). Clinically significant macular edema (CSME) was also diagnosed based on reading of the fundus photographs.

Weight, height, BMI, blood pressure, HbA_{1c}, fasting glucose, 2-h glucose (for those who had not yet developed diabetes), fasting lipid profile (total cholesterol, triglycerides, HDL cholesterol, and calculated LDL cholesterol), urinary albumin-to-creatinine ratio, and glomerular filtration rate (eGFR; based on serum creatinine as estimated with the Chronic Kidney Disease Epidemiology Collaboration equation) (16) were determined annually during DPP and DPPOS. Hypertension was defined as a blood pressure >140/90 or using antihypertension medications. Dyslipidemia was defined as LDL cholesterol >130 mg/dL, triglycerides >200 mg/dL, HDL cholesterol <40 mg/dL, or using lipid-lowering medications. Total circulating adiponectin was measured with a latex particle-enhanced turbidimetric assay (Otsuka Pharmaceutical, Tokyo, Japan). The within-run and between-run coefficients of variation for this assay are 6.21% and 9.25%, respectively. Smoking history, pregnancy history, and history of gestational diabetes were also obtained at DPP baseline and throughout the follow-up. Insulin sensitivity (1/fasting insulin and HOMA-insulin resistance) and insulin secretion (HOMA-β and insulinogenic index $[(\Delta Ins_{120} - Ins_0)/(Glu_{u120} - Glu_0)]$) were determined annually based on the glucose and insulin levels during an OGTT. Potential risk factors considered included the baseline value of all candidate risk factors as well as including the average values of weight, fasting glucose, 2-h glucose, HbA_{1c}, and systolic and diastolic blood pressure up to and including the time points at which each set of stereoscopic fundus photographs

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**A complete list of the Diabetes Prevention Program Research Group can be found in the supplementary material online.*

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Table 1—Characteristics of subjects undergoing fundus photography at each time point

	Year 1	Year 5	Year 11	Year 16
Fundus photography, *n*	899	2,128	2,086	1,563
Annual visit completed, *n*	2,645	2,528	2,273	2,051
Missing fundus photography, *n*	1,746	400	187	488
Sex				
Male	319 (35.5)	693 (32.6)	653 (31.3)	452 (28.9)
Female	580 (64.5)	1,435 (67.4)	1,433 (68.7)	1,111 (71.1)
Race/ethnicity				
Non-Hispanic White	482 (53.6)	1,138 (53.5)	1,090 (52.3)	779 (49.8)
African American	197 (21.9)	425 (20.0)	429 (20.6)	325 (20.8)
Hispanic	164 (18.2)	336 (15.8)	326 (15.6)	261 (16.7)
Asian	44 (4.9)	102 (4.8)	105 (5.0)	78 (5.0)
American Indian	12 (1.3)	127 (6.0)	136 (6.5)	120 (7.7)
Weight (kg) at baseline, mean (SD)	95.22 (20.37)	93.22 (19.27)	93.05 (19.22)	92.65 (18.60)
BMI (kg/m^2) at baseline, mean (SD)	34.21 (6.70)	33.62 (6.36)	33.62 (6.39)	33.65 (6.28)
<30	282 (31.37)	704 (33.08)	704 (33.75)	513 (32.82)
≥30	617 (68.63)	1,424 (66.92)	1,382 (66.25)	1,050 (67.18)
DPP treatment group assignment				
ILS	248 (27.6)	698 (32.8)	678 (32.5)	500 (32.0)
MET	306 (34.0)	712 (33.5)	703 (33.7)	541 (34.6)
PLB	345 (38.4)	718 (33.7)	705 (33.8)	522 (33.4)
Age (years) at baseline, mean (SD)	51.61 (10.12)	51.34 (9.95)	50.38 (9.65)	48.96 (8.99)
Age (years) at visit, mean (SD)	57.23 (10.14)	60.46 (9.94)	64.92 (9.59)	68.98 (8.98)
<45	96 (10.68)	118 (5.55)	29 (1.39)	0 (0)
45–60	458 (50.95)	960 (45.11)	617 (29.58)	245 (15.67)
≥60	345 (38.38)	1,050 (49.34)	1,440 (69.03)	1,318 (84.33)
With diabetes	595 (66.2)	956 (44.9)	1,192 (57.1)	1,026 (65.6)
HbA_{1c} (%) at baseline, mean (SD)	6.01 (0.52)	5.92 (0.49)	5.92 (0.50)	5.90 (0.49)
HbA_{1c} (mmol/mol) at baseline, mean (SD)	42.11 (5.72)	41.12 (5.39)	41.12 (5.50)	40.90 (5.39)

Data are presented as *n* (%) unless indicated otherwise.

were taken. These factors for the full cohort and for those who underwent fundus photography at each time point are shown in Supplementary Table 1.

Statistical Analysis

We used compete case analysis using all available information because there were no data missing for the risk factors in Table 1. Intent-to-treat analyses were performed for all comparisons involving the original treatment assignments. Prevalences of retinopathy at the end of the follow-up across treatment groups were compared using the Pearson χ^2 test of independence. Sensitivity analyses stratified by sex, race/ethnicity groups, age at randomization categories (<45, 45–59, ≥60 years), obesity status (baseline BMI <30 kg/m^2 or ≥30 kg/m^2), and diabetes status at the last fundus measurements were performed to examine associations between initial treatment randomizations and retinopathy risks in different subgroups. Percentages of three-step progression on a person-scale of the ETDRS or regression between two consecutive fundus examinations were compared across treatment groups using the Pearson χ^2 test at each time point. All calculations were done in SAS 9.4 software.

RESULTS

Participants

Of the 3,234 subjects randomized into DPP, 2,779 enrolled in DPPOS, and 2,499 of these underwent fundus photography at least once during DPPOS. The characteristics of these 2,499 participants at the time of each fundus photograph are shown in Table 1. Of these, retinal photography was performed in 899 (34% of those who completed that visit) at the first DPPOS visit (referred to as year 1) and was performed in 2,128 (84%), 2,086 (92%), and 1,563 (76%) at DPPOS visits years 5, 11, and 16, respectively. (The breakdown of subjects being followed and undergoing fundus photography at each time point is summarized in Supplementary Fig. 1.)

Effect of Assigned Treatment Group on the Prevalence of Retinopathy

The prevalence of diabetic retinopathy in each treatment group at DPPOS years 1, 5, 11, and 16 is shown in Fig. 1. The numbers of participants with diabetic retinopathy across all three treatment groups were 99 of 899 (11.0%), 206 of 2,128 (9.7%), 238 of 2,086 (11.4%), and 145 of 1,563 (9.3%) at years 1, 5, 11, and 16, respectively, among those who had retinal photographs at each time point. There was no difference between the prevalence of retinopathy between treatment groups at any time point (8.9% vs. 12.1% vs. 11.6% for ILS vs. MET vs. PLB, respectively, at year 1;

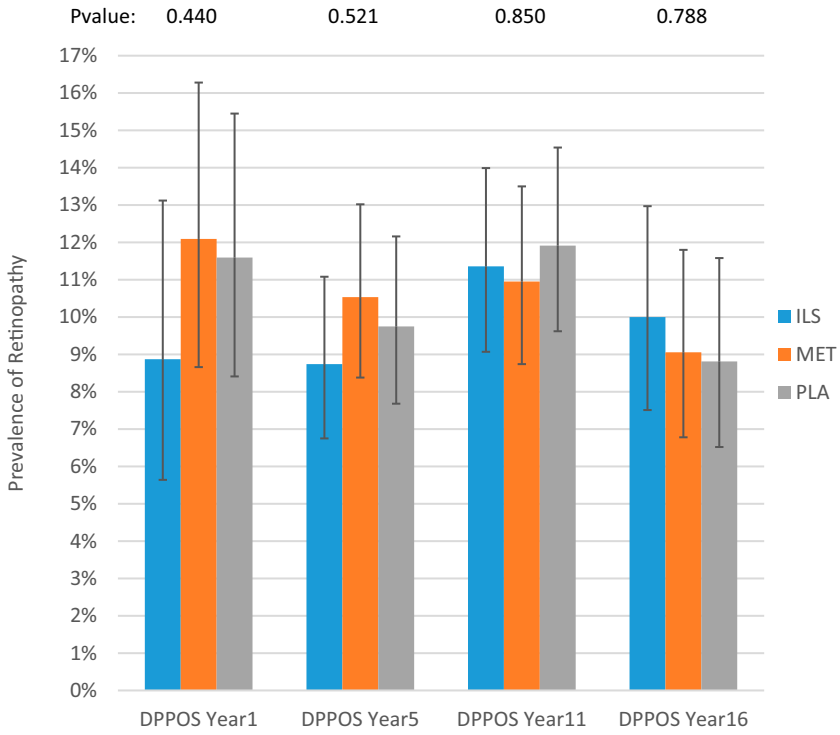

Figure 1—Prevalence of diabetic retinopathy at different time points in DPPOS by treatment group assignment at DPPOS years 1, 5, 11, and 16.

8.7% vs. 10.5% vs. 9.7% at year 5; 11.4% vs. 11.0% vs. 11.9% at year 11; and 10.0% vs. 9.1% vs. 8.8% at year 16). Of the 145 with diabetic retinopathy at year 16, 96.5% had mild nonproliferative diabetic retinopathy (NPDR; ETDRS grade 20–43), 1.4% had moderate-severe NPDR (ETDRS grade 47–61), and 2.1% had PDR (ETDRS grade 65–85) (see Supplementary Table 2). The prevalence of any retinopathy and the level of retinopathy did not differ significantly (P = 0.44–0.85) between treatment groups at any of the time points (Fig. 1).

Effect of Intervention on the Development of Diabetic Retinopathy by Subgroups

We evaluated the effect of treatment group assignment during DPP on the subsequent development of diabetic retinopathy within prespecified subgroups, including sex, race/ethnicity, BMI at entry into DPP ($<$30 kg/m^2 vs. $\geq$30 kg/m^2), and age at entry into DPP ($<$40 years, 40–65 years, $\geq$65 years). As shown in Table 2, there was no difference in the prevalence of retinopathy between treatment groups at any time point overall or within subgroups by sex (P = 0.26–0.82 for women; 0.42–0.95 for men), race/ethnicity (P = 0.08–0.86 for NHW; 0.24–0.85 for Blacks; 0.42–0.82 for Hispanics; 0.30–0.98 for American Indians; 0.37–0.79 for Asians), BMI at entry in DPP (P = 0.43–0.80 for those $<$30 kg/m^2; 0.19–0.83 for those $\geq$30 kg/m^2) or age at entry into DPP (P = 0.62–0.99 for those $<$40 years; 0.25–0.43 for those 40–65 years; 0.39–0.96 for those $>$65 years).

Effect of Metformin Administration on the Prevalence of Retinopathy During DPPOS

As noted above, based on an intention-to-treat analysis using the DPP treatment group assignment, treatment group did not have a significant effect on the prevalence of retinopathy at any time point (1, 5, 11, or 16 years) in the entire cohort or in any of our subgroup analyses (sex, race/ethnicity, baseline age, baseline BMI). However, although the exposure to metformin was markedly greater in the MET group than in the ILS or PLB groups, some subjects in the ILS or PLB groups did receive metformin by their primary physician or health care provider during DPP (because they developed diabetes) or during DPPOS (either because they developed diabetes or in hopes of slowing or preventing the onset of diabetes). Therefore, we compared the prevalence of retinopathy for those who were taking any metformin to those who were not taking metformin at the time of outcome measurements, regardless of treatment group assignment. There was no difference in the prevalence of retinopathy between those who, regardless of treatment group assignment, had received metformin and those who had not (data not shown.) This was also true within all age-group categories ($<$45 years, 45–60 years, $>$60 years). This lack of difference remained true after adjusting for potential confounders, including duration of T2D up to the time of fundus measurements, average HbA_{1c}, weight, and diastolic blood pressure during follow-up and baseline adiponectin.

Prevalence of Diabetic Retinopathy in Those With Diabetes Versus Those Without Diabetes

At the time of the last fundus photograph among the participants with at least one fundus photograph, 1,614 subjects had already developed diabetes, and 385 of these 1,614 (24%) had retinopathy; 885 still had not developed diabetes, and 127 of these 885 (14%) had developed retinopathy. The difference in retinopathy prevalence between subgroups with diabetes and prediabetes was significant at $P < 0.001$. Within the subgroups of those who had developed diabetes and those who had not yet developed diabetes, there was no difference in the prevalence of retinopathy between treatment groups. There was no difference in age, sex, race/ethnicity, or baseline BMI between those with or without T2D or between those with or without retinopathy.

Progression and Regression of Retinopathy During DPPOS

Progression of retinopathy was defined as a three-step progression between successive time points among 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) (15), and over the entire course of the follow-up among 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

Table 2—Prevalence of retinopathy by treatment group assignment by subcohorts of baseline age, sex, race/ethnicity, and baseline BMI

	DPPOS year 1			DPPOS year 5			DPPOS year 11			DPPOS year 16		
Stratum	ILS	MET	PLB	ILS	MET	PLB	ILS	MET	PLB	ILS	MET	PLB
Sample size, *n*	248	306	345	698	712	718	678	703	705	500	541	522
Age at randomization, %												
<45 years	12	7	11	10	9	10	12	12	13	11	12	10
45–59 years	8	15	11	8	11	9	11	9	12	10	7	8
≥60 years	6	11	13	9	12	11	11	15	10	10	11	11
Sex, %												
Female	8	12	10	7	9	10	10	10	12	10	9	9
Male	11	12	14	12	13	9	15	12	13	9	9	8
Race/ethnicity, %												
Non-Hispanic White	12	12	13	7	12	10	11	11	13	9	7	7
African American	6	15	13	13	10	14	15	13	13	14	12	11
Hispanic	5	9	8	9	7	5	11	13	13	11	14	11
American Indian*	0	25	0	7	5	2	4	5	0	8	8	7
Asian*	8	0	5	10	15	14	13	4	11	6	5	15
BMI at baseline, %												
<30 kg/m^2	13	12	10	9	12	10	11	11	9	6	7	10
≥30 kg/m^2	7	12	12	9	10	10	12	11	13	12	10	8
At the last fundus, %												
T2D	11	14	12	10	11	10	12	12	14	13	11	11
T2D free	3	6	9	7	9	9	10	10	7	5	6	4

P values from comparing the prevalence of retinopathy between the three treatment groups in each subgroup/stratum are all >0.05. *The American Indian group has small sample sizes at DPPOS year 1 (*n* = 2, 4, 6 for ILS, MET, PLB, respectively); the Asian group has small sample sizes at DPPOS year 1 (*n* = 13, 10, 21 for ILS, MET, PLB, respectively).

and 11, and years 11 and 16, respectively. There was no difference in progression between DPP treatment group assignments by the end of follow-up, with 3.95% in ILS, 3.35% in MET, and 4.26% in the PLB (*P* = 0.66). Regression to a lower ETDRS score did not differ by treatment groups and occurred in 8.12%, 6.55%, and 7.89%, between years 1 and 5, years 5 and 11, and years 11 and 16, respectively, in the cohort with fundus measures.

Macular Edema

CSME based on fundus photography was present in 10 participants across all four time points (2 participants at DPPOS year 1, 1 participant at DPPOS year 5, 2 participants at DPPOS year 11, and 5 participants at DPPOS year 16), and there was no difference in the prevalence of macular edema between DPP treatment group assignment.

CONCLUSIONS

We believe this to be the largest prospective, long-term longitudinal follow-up with retinal photography of a cohort of subjects at increased risk for the development of T2D. In this study, we evaluated the prevalence of retinopathy in 2,086 subjects for 11 years and in 1,553 for 16 years after completion of their participation in the DPP Study. These subjects had prediabetes (elevated fasting glucose) and impaired glucose tolerance (IGT), and BMI ≥24 kg/m^2 at the time of enrollment in DPP. The time to onset of diabetes, by American Diabetes Association criteria, was known in these subjects within a 6-month time window. This enabled the determination of the presence of diabetic retinopathy in prediabetes and from the time of biochemical onset of T2D, rather than from the time of clinical diagnosis, as has been done in most studies.

Our results show that despite reduction in the incidence of T2D by a lifestyle intervention or metformin in subjects with prediabetes, these interventions did not result in a reduction in the prevalence or severity of nonproliferative diabetic retinopathy up to 20 years later. Although the prevalence of retinopathy was lower in those who did not develop diabetes than in those who did, there was no difference in the prevalence of nonproliferative retinopathy between treatment groups regardless of diabetes status. When we explored the potential effect of the interventions in subgroups based on sex, race/ethnicity, age at entry into the DPP, or BMI at entry into the DPP, there was still no treatment effect on the prevalence of diabetic retinopathy. In addition, the use of metformin, regardless of treatment group assignment, did not have an effect on the prevalence of diabetic retinopathy.

These results are in agreement with other published studies, reviewed by Nathan et al. (12), showing that interventions that reduced the development of diabetes did not always reduce long-term microvascular complications of diabetes. Numerous studies using various interventions to prevent the development of diabetes in subjects at risk for diabetes, usually based on the presence of IGT, did not report retinopathy outcomes (17–24). The Da Qing Diabetes Prevention Outcome Study (DQDPOS), which compared a 6-year lifestyle intervention to control subjects with IGT, evaluated retinopathy after 20 and 30 years in 540 of the 577 of the randomized subjects. In this study, there was a 47% reduction (16.2% vs. 9.2%; *P* =

0.03) of severe diabetic retinopathy (vision loss, photocoagulation, or proliferative diabetic retinopathy) after 20 years (25) and a 40% reduction after 30 years (26). However, at 20 years, based on retinal photographs using a nonmydriatic camera and graded by the ETDRS system, there was no difference (38.7% vs. 36.1%; $P = 0.51$) between the intervention group and the control group in nonproliferative retinopathy (25). In our study, only 2.1% had proliferative retinopathy at 16 years, the duration of the follow-up was shorter, which may, in part, explain the different findings related to severe retinopathy. The Outcome Reduction With Initial Glargine Intervention (ORIGIN) study (27) of glargine in subjects with dysglycemia, which included nearly 1,500 subjects with IGT at baseline, showed a reduction (hazard ratio 0.90; 95% CI 0.89–0.99) in advanced complications for those with an initial HbA_{1c} >6.4%, but not in those with prediabetes (HbA_{1c} ≤6.4%; hazard ratio 1.07; 95% CI 0.95–1.20). However, this study did not separate out the various components of the microvascular outcome, so it does not provide data specifically about retinopathy.

Our study has some limitations. First, since our participants were early in the disease course, the number with retinopathy was relatively small, and thus, the power to detect group differences may be limited. We can conclude, however, that if an effect of treatment group does exist in our study, it is minor and could not be detected in a study of this size and duration. In addition, the number of subjects with proliferative retinopathy or CSME is too few to be able to show a treatment group effect on sight-threatening retinal disease.

Second, our assessment of retinopathy was based on a single set of seven-field retinal photographs at each time point. Although in the DCCT/EDIC study, in which progression of retinopathy was the primary outcome, retinopathy was classified based on two consecutive sets of photographs, most studies have used a single set of fundus photographs to define retinopathy. Indeed, at 5, 11, and 16 years, 8.1%, 6.6%, and 7.9%, respectively, had regression to a lower retinopathy grade.

Third, 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, fewer subjects were 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.

Fourth, 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.

Fifth, we do not have an ophthalmologic evaluation at the baseline visit of the DPP. Although at that time all subjects had prediabetes, without a baseline assessment, we cannot determine the incidence of retinopathy.

Lastly, although there appears to be a lower retinopathy prevalence at year 16 compared with year 11, fewer subjects were available for retinal photography at year 16 (n = 1,563) than at year 11 (n = 2,086). The percentages lost-to-follow-up and deaths do not differ across treatment groups ($P = 0.5340$).

In conclusion, in adults at risk for diabetes because of the presence of prediabetes and overweight/obesity, diabetic retinopathy begins to develop early during the course of dysglycemia, occurring during the prediabetic phase and before the diagnosis of diabetes based on currently accepted criteria. Although interventions during the prediabetic phase influence the incidence of developing diabetes, such treatments did not reduce the prevalence of sight-threatening retinopathy after 20 years of follow-up. Since interventions that reduce the development of diabetes do not appear to reduce the subsequent development of long-term diabetes-related retinopathy, and since retinopathy is invariably mild and of little clinical consequence, screening for retinal changes in persons with prediabetes does not seem to be warranted based on currently available data. Whether interventions to reduce plasma glucose or other metabolic abnormalities during the prediabetic phase will alter the course of long-term complications requires further study.

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