Retinopathy in Youth With Type 2 Diabetes Participating in the TODAY Clinical Trial

TODAY Study Group*

OBJECTIVE—To determine the prevalence of retinopathy in 517 youth with type 2 diabetes of 2–8 years duration enrolled in the TODAY study.

RESEARCH DESIGN AND METHODS—Retinal photographs were graded centrally for retinopathy using established standards.

RESULTS—Retinopathy was identified in 13.7% of subjects. Prevalence increased with age, diabetes duration, and mean HbA_{1c}. Subjects in the highest BMI tertile had the lowest prevalence of retinopathy.

CONCLUSIONS—Prevalence of retinopathy and its association with HbA_{1c} and diabetes duration is similar to that previously reported in youth with type 1 diabetes and in adults with type 2 diabetes of known duration. The mechanism underlying the reduced risk of retinopathy in the most obese individuals is unknown. Follow-up of this cohort will help define the natural history of retinopathy in youth with type 2 diabetes.

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Characterization of the early course of diabetic retinopathy in adults with type 2 diabetes has been hindered by the long lag time before diagnosis. The TODAY cohort of youth with type 2 diabetes is ideal for examining the prevalence of retinopathy early in the course of the disorder.

RESEARCH DESIGN AND METHODS

The TODAY clinical trial enrolled 699 youth with type 2 diabetes who were 10–17 years of age. Subjects were randomized to treatment with metformin alone, metformin plus rosiglitazone, or metformin plus intensive lifestyle intervention, and they were followed-up for 2–6.5 years (1). The TODAY CONSORT Diagram is shown in Supplementary Fig. 1. In the last year, retinal examinations were obtained for 524 participants and 517 had digital fundus photographs of seven standard stereoscopic fields that were readable in at least one eye. The Fundus Photograph Reading Center at the University of Wisconsin certified retinal photographers at participating sites, and photographs were evaluated centrally by experienced graders according to an abbreviated and modified version of the Early Treatment Diabetic Retinopathy Study Final Retinopathy Severity Scale for Persons; the scale has 17 steps, ranging from no retinopathy in either eye to high-risk proliferative retinopathy in both eyes (2).

Because no subjects had more than mild nonproliferative retinopathy (NPDR), they were coded only as having or not having retinopathy. The minimum level of retinopathy was at least one retinal lesion (microaneurysm, intraretinal hemorrhage, or cotton wool infarct) in at least one eye. Associations among retinopathy, age, diabetes duration, treatment arm, race/ethnicity, sex, and mean HbA_{1c} and BMI during the study were examined. Each continuous variable of interest was divided into categories based on tertiles. Odds ratios (ORs) and 95% CIs, adjusted for patient age, mean HbA_{1c}, and months since diagnosis, were calculated for each variable of interest using the first tertile as the comparison group for all calculations. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Data are presented as mean ± SD.

RESULTS

The characteristics of the young people in the TODAY study have been previously described (3). All participants were overweight or obese, 64.4% were female, and >80% were from racial/ethnic minority groups. The demographics of the subjects with readable fundus photographs did not differ from the larger group. Age at time of examination was 18.1 ± 2.5 years, diabetes duration was 4.9 ± 1.5 years (range, 2.0–8.4), HbA_{1c} was 7.1 ± 1.7% (54 ± 5 mmol/mol), and BMI was 36 ± 8 kg/m^2.

Of 517 participants, 71 had early retinopathy, with 64 having very mild NPDR (only microaneurysms or other vascular pathology such as intraretinal hemorrhage or cotton wool infarct), and 7 having mild NPDR (microaneurysms plus other vascular pathology). Of those with very mild NPDR, 46 had findings in only one eye. Of those with mild NPDR, five had mild findings in both eyes, one had involvement of a single eye, and another had very mild NPDR in the second eye. None had macular edema, advanced NPDR, or proliferative retinopathy. Lesions observed in individual eyes are shown in Supplementary Table 1. Using adjusted ORs, sex, treatment group, ethnicity, blood pressure, smoking, pregnancy, microalbuminuria, and lipids did not affect retinopathy. Compared with the group without retinopathy, participants with retinopathy had higher HbA_{1c} (8.3 ± 1.77 [67 ± 4] vs. 6.9 ± 1.60% [52 ± 6 mmol/mol]; $P < 0.0001$),

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*A complete list of the members of the TODAY Study Group can be found in the Supplementary Data online. The members of the writing group are listed in the APPENDIX.

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longer duration of diabetes (5.59 ± 1.28 vs. 4.74 ± 1.46 years; $P < 0.0001$), and were older (19.1 ± 2.08 vs. 17.9 ± 2.47 years; $P = 0.0001$). Adjusted ORs confirmed these findings (Table 1). Retinopathy was less common in subjects in the highest BMI tertile.

CONCLUSIONS—In TODAY, the prevalence of early retinopathy in young people with a mean duration of type 2 diabetes of 4.9 years was 13.7%. This is higher than previously reported in young Pima Indians, in whom retinopathy was detected only after age 20 years and who had diabetes >5 years. Retinopathy in that study was determined by dilated direct ophthalmoscopy, rather than by standardized fundus photographs assessed by skilled graders (4). In the SEARCH study, the prevalence of retinopathy using retinal photography was 17% for type 1 diabetes and 42% for type 2 diabetes. However, participants in the SEARCH study had known diabetes duration >5 years (mean duration, 7.2 years) and were older (mean age, 21 years) (5). A small Australian study of adolescents with type 2 diabetes <2 years reported a retinopathy prevalence of only 4% (6). Differences in methodology in these studies make direct comparisons difficult. However, retinopathy prevalence in adults who developed diabetes on follow-up in the Diabetes Prevention Program was 15.5% after slightly more than 3 years of diabetes (7). This is similar to our data obtained using the same techniques.

As in adults, increased prevalence of retinopathy in TODAY participants was associated with older age, longer diabetes duration, and glycemic control as assessed by HbA_{1c}. The most severely obese individuals had decreased retinopathy. An association of lower weight or BMI with increased retinopathy has been reported previously in adults with type 2 diabetes and has been attributed to poor diabetes control (8). In our subjects, lower BMI was a risk factor for retinopathy even after controlling for HbA_{1c}. This has not been previously reported in young people with type 2 diabetes. Decreased retinopathy prevalence has been linked with increased BMI, C-peptide, and C-reactive protein (9,10). This suggests a protective effect of insulin resistance, given the association of insulin and IGF-I with development of diabetic eye disease (11). Abdominal obesity may be protective compared with more generalized obesity (12). This "obesity paradox" has been recognized previously in studies of adult mortality from heart failure, hypertension, and other conditions (13). Understanding the association might help to elucidate mechanisms of the development of retinopathy and separate the effect of hyperglycemia from direct effects of insulin or the inflammatory effects of obesity.

A limitation of this study is that retinal photographs were obtained only at the end of the TODAY trial because the burdens and complexity of the clinical trial precluded baseline eye assessments (3). However, continued follow-up of the TODAY cohort will allow us to define the natural history and progression of retinopathy in this large population of youth with type 2 diabetes.

APPENDIX—The members of the writing group are as follows: Lynne L. Levitsky (chair), MD, Massachusetts General Hospital; Ronald P. Danis, MD, University of Wisconsin; Kimberly L. Drews, PhD, George Washington University; William V. Tamborlane, MD, Yale University School of Medicine; Morey W. Haymond, MD, Baylor College of Medicine; Lori Laffel, MD, Joslin Diabetes Center; and Terri H. Lipman, PhD, Children's Hospital of Philadelphia.

Table 1—*Adjusted ORs for diabetic retinopathy based on tertile of mean HbA_{1c}, age at fundus photograph, months since diagnosis, and mean BMI*

	Overall	Diabetic retinopathy		Adjusted	
	N	*N*	%	OR	95% CI
Mean HbA_{1c}*					
4.30–5.92% (23–41 mmol/mol)	172	8	4.7		
5.93–7.80% (41–62 mmol/mol)	173	20	11.6	2.497	1.058–5.894
7.81–13.50% (62–124 mmol/mol)	172	43	25.0	6.311	2.840–14.023
Age at fundus photograph, years†					
12–16	140	8	5.7		
17–18	137	17	12.4	1.952	0.784–4.857
19–24	240	46	19.2	3.005	1.270–7.112
Months since diagnosis‡					
24–49	170	9	5.3		
50–66	172	23	13.4	1.974	0.842–4.628
67–101	175	39	22.3	3.649	1.504–8.848
Mean BMI, kg/m^2§					
21.60–31.50	172	28	16.3		
31.50–37.86	173	27	15.6	0.756	0.403–1.417
37.87–68.70	172	16	9.3	0.552	0.377–0.810

*ORs adjusted for age at photograph and months since diagnosis only. †ORs adjusted for mean HbA_{1c} and months since diagnosis only. ‡ORs adjusted for age at photograph and mean HbA_{1c} only. §ORs adjusted for age at photograph, mean HbA_{1c}, and months since diagnosis.

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L.L.L. researched data, contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. R.P.D. researched data, contributed to the discussion, and reviewed and edited the manuscript. K.L.D. researched data, wrote the manuscript, and reviewed and edited the manuscript. W.V.T. researched data, contributed to the discussion, and reviewed and edited the manuscript. M.W.H. contributed to the discussion and reviewed and edited the manuscript. L.L. researched data, contributed to the discussion, and reviewed and edited the manuscript. T.H.L. contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript. K.L.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at https://today.bsc.gwu.edu/.

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