Prevalence and Significance of Retinopathy in Subjects With Type 1 Diabetes of Less Than 5 Years’ Duration Screened for the Diabetes Control and Complications Trial

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OBJECTIVE — The Diabetes Control and Complications Trial (DCCT) demonstrated the powerful impact of glycemic control on the progression of diabetic retinopathy. A large number of individuals (2,771) underwent stereoscopic color photography and fluorescein angiography as part of screening for participation in the DCCT. A subgroup of those individuals screened participated in the DCCT and underwent evaluation of their retinal vasculature semiannually for 4–9 years. These data were evaluated to determine how the 2000 American Diabetes Association position statement would apply to the DCCT experience. Specifically, the position statement indicates that the first dilated eye examination should be performed after 3–5 years’ duration of diabetes because vision-threatening retinopathy virtually never develops in patients with type 1 diabetes during that interval.

RESEARCH DESIGN AND METHODS — We examined the experience of the DCCT in evaluating retinal photographs in 1,613 patients with type 1 diabetes of <5 years’ duration and follow-up photographs every 6 months for 4–9 years in 855 members of that group.

RESULTS — Of 1,613 subjects with type 1 diabetes of <5 years’ duration screened for the DCCT, 716 (44.4%) had stereo-color photographic evidence of diabetic retinopathy, and 6 had preproliferative or worse pathology. Fluorescein angiography revealed retinopathy in 158 of 713 subjects with no evidence of retinopathy on color photographs. Thus, 874 (54.2%) of the original 1,613 subjects had retinopathy at baseline. DCCT follow-up identified 341 additional individuals in whom retinopathy was developing before 5 years; 1,083 of 1,613 (67.1%) individuals screened for the DCCT had retinopathy before 5 years’ duration of diabetes. Those with retinopathy before 3 years had more rapid three-step progression of vascular pathology than those with no retinopathy.

CONCLUSIONS — Dilated eye examinations and retinal photography should be included in the routine management of type 1 diabetes during the first 5 years to identify the individuals at greatest risk for vision-threatening problems.


Diabetic retinopathy is a highly specific microvascular complication of diabetes. The prevalence of retinopathy is directly related to the duration of diabetes. The 2000 American Diabetes Association (ADA) position statement on diabetic retinopathy (1) indicates that vision-threatening retinopathy does not occur in patients with type 1 diabetes during the first 3–5 years’ duration of the disease; therefore, an initial retinal examination should be performed within 3–5 years after the initial diagnosis. The ADA recommendation also indicates that nearly all patients with type 1 diabetes have retinopathy after 20 years’ duration of diabetes. Overall, diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness in the U.S. among adults aged 20–74 years. Observations that lead to a reduction of this common public health problem are of great importance. The Diabetes Control and Complications Trial (DCCT) was designed to assess whether a treatment regimen aimed at achieving blood glucose values as close to the nondiabetic range as possible would reduce the onset and progression of the retinal vascular abnormalities. The conclusion was affirmative (2). The rigorous retinal examinations performed during the DCCT may provide useful documented clinical measurements to evaluate the ADA recommendations for diabetic retinopathy.

Color photography and fluorescein angiography are two methods used to document vascular abnormalities in the eye. Both of these techniques are more sensitive than direct clinical examination (3–4). The DCCT used stereoscopic color retinal photography and fluorescein angiography to screen patients before entry into the study; that experience indicated that fluorescein angiography was more sensitive than stereoscopic color photographs for the detection of retinopathy (5). It was concluded, however, that fluorescein angiography was useful for detecting the earliest vascular abnormalities, but the importance of this capability was of little clinical utility. Fluorescein angiography was performed during the screening of volunteers, but no follow-up fluorescein studies were performed. This...
Table 1—Diabetic retinopathy scale and screening results for the DCCT

<table>
<thead>
<tr>
<th>Level</th>
<th>Severity</th>
<th>Definition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>No retinopathy</td>
<td>Diabetic retinopathy absent</td>
<td>897</td>
</tr>
<tr>
<td>20</td>
<td>Very mild nonproliferative diabetic retinopathy</td>
<td>Microaneurysms only</td>
<td>482</td>
</tr>
<tr>
<td>35</td>
<td>Mild nonproliferative diabetic retinopathy</td>
<td>Microaneurysms plus hard exudates, soft exudates and/or mild retinal hemorrhages</td>
<td>145</td>
</tr>
<tr>
<td>43</td>
<td>Moderate nonproliferative diabetic retinopathy</td>
<td>Microaneurysms plus mild intraretinal microvascular abnormalities or moderate retinal hemorrhages</td>
<td>69</td>
</tr>
<tr>
<td>47</td>
<td>Moderate nonproliferative diabetic retinopathy</td>
<td>More extensive intraretinal microvascular abnormalities, severe retinal hemorrhages, or venous beading in one quadrant only</td>
<td>13</td>
</tr>
<tr>
<td>53</td>
<td>Severe nonproliferative diabetic retinopathy</td>
<td>Severe retinal hemorrhages in four quadrants, or venous beading in at least two quadrants, or moderately severe intraretinal microvascular abnormalities in at least one quadrant</td>
<td>1</td>
</tr>
<tr>
<td>61</td>
<td>Mild proliferative diabetic retinopathy</td>
<td>New vessels elsewhere &lt;1/2-disc area in one or more quadrants, or greater including new vessels on or within 1-disc diameter of optic nerve and/or vitreous hemorrhage</td>
<td>6</td>
</tr>
</tbody>
</table>

TOTAL: 1,613

report examines the experience of the DCCT in evaluating retinal photographs in 1,613 patients with type 1 diabetes of <5 years' duration and follow-up photographs every 6 months for 4–9 years in 855 members of that group.

**RESEARCH DESIGN AND METHODS** — The DCCT screened 2,771 volunteers to participate in the multicentered clinical trial to test the influence of blood glucose levels on the progression of retinopathy in subjects with type 1 diabetes. Type 1 diabetes was defined as ≥1 year of continuous insulin treatment with a demonstrated inability to secrete C-peptide after a liquid meal (Sustacal) (2).

After the initial screening, the study participants were placed in two different study groups. The primary prevention cohort were individuals with type 1 diabetes of 1–5 years’ duration who had no retinopathy observed on stereoscopic color photography, best corrected visual acuity in each eye of 20/25 or better (EDRS charts), and urinary albumin excretion <40 mg/24 h. The secondary intervention cohort had a duration of diabetes of 1–15 years, very mild (microaneurysms only) to moderate nonproliferative diabetic retinopathy, best visual acuity in each eye of 20/32 or better, and urinary albumin excretion ≥200 mg/24 h. Retinopathy was assessed as previously described (2). These data were recorded at the Data Coordinating Center of the DCCT and made available to the medical community at the conclusion of the study.

**Data analysis and statistics.** Data were received from the DCCT’s Data Coordinating Center (George Washington University, Rockville, MD). Information regarding each subject’s baseline characteristics (duration of type 1 diabetes, retinopathy status, retinopathy detection method, HbA1c, treatment group, and the follow-up [retinopathy and HbA1c progression over time]) was extracted.

A subset of subjects with type 1 diabetes of <5 years’ duration at baseline was identified. Kaplan-Meier curves and log-rank tests were performed to test for a difference in retinopathy progression when grouped by baseline retinopathy status. Additionally, for those with retinopathy at baseline, similar analyses were performed to test for a difference in retinopathy progression associated with the method of baseline retinopathy detection (e.g., color photography or fluorescein angiography). This analysis was repeated, subsetting the data further for those subjects with baseline retinopathy detected by fluorescein angiography only. Kaplan-Meier curves and log-rank tests were performed to test for a difference in retinopathy progression by treatment group. The reduced number of subjects in this subset reduced the power of these observations to show a treatment effect of 45%. Statistical significance was accepted at 5% throughout.

**RESULTS** — There were 1,613 individuals with type 1 diabetes of ≤5 years’ duration who had seven-field stereoscopic color retinal photographs taken as part of the screening for admission into the DCCT. The Final Diabetic Retinopathy Scale used in the DCCT (6) is seen in Table 1. Of the 1,613 subjects, 897 subjects (55.6%) had no evidence of microvascular disease on retinal stereoscopic color photographs, whereas 716 (44.4%) had photographic evidence of microvascular abnormalities (Table 1). Six of 716 individuals with retinopathy and diabetes of <5 years’ duration had preproliferative or worse retinopathy identified on the color photographs. Of the 1,613 subjects, 234 subjects (14.5%) with type 1 diabetes of <5 years’ duration had microaneurysms plus exudates and mild retinal hemorrhages or worse at entry into the DCCT. Of the 1,613 subjects, 482 subjects (29%) had only microaneurysms as evidence of retinopathy at entry. Of the group of 897 subjects with no evidence of retinopathy on stereoscopic color photographs, 713 subjects were chosen to be the primary prevention (no observed microaneurysms) cohort. Fluorescein angiography, however, revealed mild retinopathy (5) in 158 of 713 subjects (22.2%) of that primary prevention group.
The addition of the fluorescein-positive patients (158) to the group with retinopathy on color photographs (716) results in 874 of the 1,613 subjects (54.1%) having retinopathy at DCCT baseline and before 5 years’ duration of diabetes. The observed pathology may have been greater if we knew the results of the fluorescein studies on the 184 subjects with type 1 diabetes of 5 years’ duration who were not included in the DCCT study group, but this information was not available to the authors. Retinopathy was observed in 19.4% of the DCCT subjects with diabetes of 1 year duration; this progressively increased with time to 48.4% of those subjects with diabetes of 4–5 years’ duration (Table 2).

Of the 855 subjects with diabetes of <5 years’ duration, 713 had no evidence of retinopathy on stereoscopic color photographs at DCCT baseline. During the follow-up in the DCCT, sustained retinopathy (recorded on color photographs) developed in 341 subjects with diabetes before 5 years’ duration. Microaneurysms, exudates, mild hemorrhages, or worse had been observed in 30 of those subjects before 5 years’ duration of diabetes. The progression to retinopathy noted during the follow-up of 713 individuals without retinopathy at baseline increased the incidence occurring before 5 years’ duration of diabetes by 341 subjects. The combination of 716 retinopathy positive color photographs at baseline plus 341 converters before 5 years’ duration of diabetes plus 26 noted on fluorescein study alone between 4 and 5 years’ duration (not counted as converters) produced a total of 1,083 of 1,613 subjects with type 1 diabetes (67.1%) with retinopathy before 5 years’ duration of diabetes. Subjects in whom retinopathy developed during the first 4 years’ duration of diabetes had three-step progression of retinopathy at the rate of 4.2 events per year, whereas subjects with no evidence of retinopathy during the first 4 years’ duration of diabetes progressed at the rate of 3.2 events per year ($P < 0.02$) (Fig. 1). Two of the 555 individuals (0.4%) with no evidence of retinopathy and diabetes duration <5 years at baseline progressed to retinopathy requiring laser treatment during the 5–9 years of DCCT follow-up, whereas 9 of 142 individuals who had retinopathy before 5 years’ duration of diabetes at DCCT baseline progressed to pathology.

![Figure 1](image-url)  
**Figure 1**—The rate of three-step progression of diabetic retinopathy. A comparison of the probability for no progression between those who had no evidence of retinopathy on color photographs during the first 4 years’ duration of clinical diabetes to those who had evidence of retinopathy before 4 years’ duration of diabetes. ———, some evidence; –– ––, no evidence. $P = 0.020$ by log-rank test.

<table>
<thead>
<tr>
<th>Duration of diabetes (years)</th>
<th>Retinopathy</th>
<th>Fluorescein angiography</th>
<th>Total</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>On color photographs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>3</td>
<td>36</td>
<td>19.4</td>
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<td>2</td>
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<td>4</td>
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<td>27</td>
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<td>42.2</td>
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<td>&lt;5</td>
<td>79</td>
<td>48</td>
<td>153</td>
<td>48.4</td>
</tr>
<tr>
<td>TOTAL:</td>
<td>555</td>
<td>142</td>
<td>855</td>
<td>35.1</td>
</tr>
</tbody>
</table>

Retinopathy status for DCCT study subjects at baseline (Table 2).
Those individuals with <5 years' duration of diabetes who had initial vascular abnormalities noted only on fluorescein angiography seemed to have faster progression of retinal pathology documented on color photographs than those identified at baseline by retinal color photographs (Fig. 2). Those individuals who had retinopathy seen only on fluorescein angiography had not only more rapid progression of pathology, but they also had no apparent benefit from intensified therapy as used in that group of patients \((P < 0.09)\). This occurred even though experimental therapy resulted in a significant reduction in the HbA1c for that group.

CONCLUSIONS — The 2000 ADA position statement on diabetic retinopathy indicates that a dilated eye examination should be performed within 3–5 years of the diagnosis of type 1 diabetes (1). The ADA position statement implies that because vision-threatening retinopathy does not occur in patients with type 1 diabetes during the first 3–5 years' duration of the disease, formal dilated eye examinations and certainly fluorescein angiography are not clinically indicated. The individuals who volunteered to participate in the DCCT were a special group with greater interest and availability to specialized treatment and management of type 1 diabetes, but there was no recognized biologic bias. This cross-sectional survey of 1,613 subjects with type 1 diabetes of <5 years' duration is much larger than the 137 subjects evaluated in the population-based Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) (7). The percentage of DCCT volunteers with type 1 diabetes of <5 years' duration that had retinopathy was at least 67.1%, which is higher than the 49.0% positive findings reported in subjects with type 1 diabetes of ≤4 years' duration reported in the WESDR study (7). Our data differ from WESDR because we had follow-up evaluations during the first 5 years' duration of diabetes in the 713 individuals with no retinopathy at baseline. Both the DCCT and the WESDR data differ from earlier reports that indicate a low prevalence of retinopathy during the first 5 years' duration of type 1 diabetes (8,9). The observation that 20% of the DCCT volunteers with diabetes of 1 year duration had retinopathy suggests that dilated eye examinations should be performed during the first year after diagnosis of type 1 diabetes. Although the retinopathy noted at 1 year was microaneurysms alone, a recent report from the UKPD Study Group (10) indicates that the finding of one or two microaneurysms in an eye is important for predicting progression of retinopathy. If one evaluates the rate of three-step progression, those with early retinopathy (<5 years' duration) progress faster than those with no retinopathy after 4 years' duration of diabetes (Fig. 1). There is some concern about the utility of recognizing the earliest vascular pathology using fluorescein angiography (5). The DCCT data indicate that subjects who had microaneurysms noted only on fluorescein angiography were those who had the most rapid three-step progression of retinopathy, which may mean that this diagnostic study has importance for identifying subjects at the greatest risk for progressive retinopathy. It was also noted that the experimental "intensified" therapy used in the DCCT had little beneficial effect in slowing the progression of retinopathy in that subgroup of patients. This may represent a problem of subgroup analysis of a larger study, or it may indicate that these patients need more aggressive or different therapy and deserve more careful evaluation to determine how they should be managed to prevent "vision-threatening retinopathy." Our observation that laser...
Retinopathy in type 1 diabetes of <5 years' duration

treatment was required for 6.3% of those with photographic evidence of retinopathy before 5 years' duration of diabetes, whereas those with no evidence of retinopathy before 5 years' duration of diabetes had only 0.4% progress to pathology requiring laser treatment, supports the idea that those with early retinopathy have more rapid progression to vision-threatening pathology. Of the 1,613 individuals with diabetes of <5 years' duration who were screened, six subjects had preproliferative or greater retinopathy. Although this is a small number, it underlines the risk of indicating that vision-threatening retinopathy does not occur before 3–5 years' duration of type 1 diabetes (1). Of the 855 subjects with type 1 diabetes of <5 years' duration followed in the DCCT, retinopathy developed in 483 subjects (56.5%) during the first 5 years; 429 of those volunteers underwent retinal photography before 3 years' duration of diabetes, and results were positive in 109 subjects (25.4%). Six randomized DCCT volunteers had microaneurysms plus exudates and mild retinal hemorrhages, whereas three more subjects had intraretinal microvascular abnormalities and moderate retinal hemorrhages before 3 years' duration of diabetes. These more advanced stages of retinopathy were found in 2.1% of the individuals selected as having no retinopathy at DCCT baseline.

Analysis of the DCCT data suggests that the benefit of reduced progression of retinopathy is enhanced by early implementation of the experimental “intensified” therapy (6). Early dilated eye examinations could help underline the importance of intensified therapy for patients with type 1 diabetes. It may also identify individuals who have early retinopathy and are at greatest risk for progression. This may be important for the effective allocation of limited personnel resources required for the implementation of the intensified therapy employed by the DCCT study group.

Photographic evidence of diabetic retinopathy was found in 67.1% of 1,631 subjects with type 1 diabetes of <5 years' duration who were screened for participation in the DCCT. These data were generated by a blinded group of expert readers at a central site that was not participating in the care of the subjects and should eliminate any potential bias. Subjects in whom retinopathy developed before 5 years' duration of diabetes (early retinopathy) had a more rapid three-step progression of retinal pathology. The large frequency of early retinopathy in patients with type 1 diabetes makes dilated eye examinations, even during the first year after diabetes is diagnosed, important for the informed care of patients. Because 3–5 years of intensified therapy are required to reduce the rate of progression of retinopathy (2), it would be important to make patients with early pathology aware of their situation, because they seem to progress at a faster rate. The observation of more rapid progression of pathology in individuals identified with early retinopathy only on fluorescein angiography deserves further evaluation to determine whether this identifies a unique mechanism. Serum samples from these subjects are available from the DCCT to test appropriate hypotheses.

In conclusion, retinopathy is common during the first 5 years' duration of type 1 diabetes. Early recognition will identify patients at high risk, who will have the greatest benefit from the intensified therapy used by the DCCT Study Group. Annual dilated eye examinations and possibly retinal photography should be the standard of care implemented from the onset of type 1 diabetes and not delayed for 3–5 years.

Acknowledgments — We thank Patricia A. Cleary, MS, Director of the DCCT Data Coordinating Center at George Washington University, Rockville, MD, for providing the screening data for the DCCT volunteers. This study was presented, in part, at the 60th scientific sessions of the American Diabetes Association, San Antonio, Texas, 9–13 June 2000.

References