ABSTRACT

Several factors have been correlated with diabetic retinopathy (DR), including glycemic control, hypertension, lipid profiles, carotid disease, pregnancy, nephropathy, and anemia. In the 1990s, the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the importance of the relationship between glycemic control and DR, specifically whether intensive glycemic control could retard the progression of DR. Additionally, the UKPDS-38 study examined the role of hypertension in the management of DR. Data have indicated that maintaining hemoglobin A1c levels of less than 7%, fasting plasma glucose of less than 110 mg/dL, systolic blood pressure of less than 130 mm Hg, and diastolic blood pressure of less than 85 mm Hg slow the progression of microvascular complications, specifically DR. Despite the importance of monitoring DR, 30% to 50% of patients do not receive adequate screening because of perceived inconvenience, limited access, and concerns over cost. Available screening options are highly sensitive and highly specific in the research environment, but are technique-dependent and may not be applicable in large patient populations. Additionally, comprehensive ophthalmic examinations are imperative to the diagnosis of other treatable eye diseases, including cataracts and glaucoma. Ophthalmologists encounter diabetes in their patients on a regular basis. Taking a proactive role in their patients’ ocular health and overall metabolic health may encourage patients to also be proactive in the management of their own health.


Ophthalmologists encounter diabetes in their patients on a regular basis. Because appropriate medical management is critical to the treatment of diabetic retinopathy (DR), ophthalmologists have the opportunity not only to impact patients’ ocular health but also to improve their overall health. Several systemic factors have been correlated to the development and progression of DR, including poor glycemic control, hypertension, hyperlipidemia, carotid artery disease, pregnancy (which is important in a relatively small subset of patients), nephropathy, and anemia.

Two major trials completed in the 1990s—the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS)—demonstrated the importance of the relationship between glycemic control and DR. The DCCT examined patients with type 1 diabetes and the UKPDS examined patients with type 2 diabetes; both studies sought to answer whether intensive glycemic control could retard the progression of a variety of microvascular and macrovascular complications, including DR.
DIABETES CONTROL AND COMPLICATIONS TRIAL AND OUTCOMES

The DCCT was a multicenter clinical trial that included 2 cohorts—a primary-prevention cohort that evaluated the effect of glycemic control on the progression of DR in patients who had no DR at the time of study enrollment ($n = 726$), and a secondary-intervention cohort that examined the effect of glycemic control over time in patients who had already been diagnosed with relatively mild DR ($n = 715$). All patients were randomly assigned to intensive therapy (administered by an external insulin pump or ≥3 daily insulin injections) or to conventional therapy with 1 or 2 daily insulin injections. The appearance and progression of retinopathy was assessed regularly over a mean of 6.5 years.¹

In the primary-prevention cohort, intensive glycemic control reduced the risk of developing DR by 76%. In the secondary-intervention cohort, intensive glycemic control slowed the progression of DR by 54%, in addition to reduced the development of proliferative DR, or severe nonproliferative DR, by 47%. Notably, a short-term worsening of DR was seen in the first 2 years of the study among the intensive control patients in the secondary-intervention cohort.¹⁸ In the first year, approximately 22% of these patients had a 3-step change in their DR on a modified Early Treatment Diabetic Retinopathy Study (ETDRS) scale compared to an estimated 13% of patients in the conventional group. However, by month 18 of the study, that trend was reversed, and 3 years onward, the benefits of intensive control were consistent. The DCCT also analyzed the patients' hemoglobin (Hb) $A_1C$ levels, with the optimal goal being an Hb$A_1C$ of 7% or less. Patients in the conventional treatment group had a clearly suboptimal mean Hb$A_1C$ of 9.1% at the study’s end. In marked contrast, the mean Hb$A_1C$ was 7.2% in the intensive treatment group (Table 1).¹³ These Hb$A_1C$ results raise 2 important points: even with intensive glycemic control, it can be extremely difficult to achieve ideal Hb$A_1C$ levels, and it is imperative that ophthalmologists impress upon their patients the importance of the link between glycemic control and ocular health.

UNITED KINGDOM PROSPECTIVE DIABETES STUDY AND OUTCOMES

The multicenter UKPDS study included 3867 patients newly diagnosed with type 2 diabetes.² Similar to the DCCT, patients were randomized to an intensive treatment group ($n = 2729$) or a conventional treatment group ($n = 1138$). The UKPDS results also showed that intensive therapy reduced the risk of developing DR by 52% and slowed the progression of DR by 54% compared to the conventional group. These findings highlight the importance of early intervention in diabetes management to prevent or delay the onset of DR.

Table 1. Summary of Selected DCCT Data*

<table>
<thead>
<tr>
<th>Question Addressed</th>
<th>Findings</th>
<th>$P$ Value</th>
</tr>
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<tbody>
<tr>
<td>Will intensive glycemic control reduce the risk of</td>
<td>With intensive glycemic control:</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>retinopathy onset in type 1 diabetes?</td>
<td>76% risk reduction of DR onset</td>
<td></td>
</tr>
<tr>
<td>Will intensive glycemic control reduce the risk</td>
<td>With intensive glycemic control:</td>
<td>≤.002</td>
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<tr>
<td>of progression of NPDR in type 1 diabetes?</td>
<td>54% risk reduction in the progression of DR in secondary-intervention</td>
<td></td>
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<tr>
<td></td>
<td>group</td>
<td></td>
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<td></td>
<td>47% risk reduction in the development of severe NPDR or proliferative DR</td>
<td>.011</td>
</tr>
<tr>
<td>Does intensive glycemic control increase the risk of</td>
<td>With intensive glycemic control:</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>early worsening of DR?</td>
<td>Two times greater occurrence of early worsening</td>
<td></td>
</tr>
<tr>
<td>Do patients benefit from intensive glycemic control,</td>
<td>With intensive glycemic control:</td>
<td>.03</td>
</tr>
<tr>
<td>despite early worsening of DR?</td>
<td>65% risk reduction in the progression of DR,</td>
<td></td>
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<tr>
<td></td>
<td>despite early worsening</td>
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</table>

* $n = 1441$.

¹Progression of retinopathy: ≥3-step change in Early Treatment Diabetic Retinopathy Study retinopathy grade from baseline sustained at least 6 months evaluated using stereo fundus photography.

²DCCT = Diabetes Control and Complications Trial; DR = diabetic retinopathy; NPDR = nonproliferative diabetic retinopathy.

group \((n = 1138)\). Those patients receiving intensive treatment used a sulfonylurea or insulin, whereas those in the conventional treatment group attempted to control their HbA1c with diet. The UKPDS compared the effects of these treatments on the risk of microvascular and macrovascular complications.

The resulting changes in the median HbA1c in this study were not as substantial as those noted in the DCCT; over 10 years, median HbA1c was 7.0% in the intensive treatment group compared to 7.9% in the conventional treatment group. Interestingly, the HbA1c levels consistently deteriorated over time, thus by the completion of the study, most patients showed evidence of increasing HbA1c levels. Nonetheless, the risk reduction for diabetic microvascular complications was impressive—a 25% risk reduction in microvascular endpoints, a 29% reduction in need for retinal photocoagulation, a 17% risk reduction for progression of DR, and a 24% reduction for cataract extraction occurred (Table 2).

In addition to effects of treatments on HbA1c, the UKPDS also examined the influence of hypertension management on DR. A total of 1148 hypertensive patients with type 2 diabetes were allocated to intensive hypertension control \((n = 758)\) or to conventional hypertension control \((n = 390)\). Mean blood pressure during follow-up was significantly reduced in patients assigned to intensive hypertension control \((144/82 \text{ mm Hg})\) compared to patients assigned to conventional control \((154/87 \text{ mm Hg})\). Risk reductions in patients assigned to intensive hypertension control were impressive at 37% and 35% for microvascular complications and retinal photocoagulation, respectively. Additionally, data indicated that the retinopathy of 37% of patients in the captopril group and 37% of patients in the atenolol group had progressed 2 or more steps, whereas 51% of patients in the conventional treatment group experienced this level of deterioration.

How then should ophthalmologists approach the diabetic condition? Few ophthalmologists take an active role in the management of their patients’ diabetes in terms of glycemic control or hypertension; however, as physicians, they can educate patients on data from the DCCT and UKPDS studies. Furthermore, they can encourage patients to reach and maintain HbA1c levels of less than 7%, fasting plasma glucose of less than 110 mg/dL, systolic blood pressure of less than 130 mm Hg, and diastolic blood pressure of less than 85 mm Hg to slow the progression of microvascular complications, specifically DR.

### Diabetic Retinopathy and Dyslipidemia

Diabetes is frequently associated with the presence of dyslipidemia, which includes elevated total cholesterol levels, low-density lipoprotein, triglycerides, and decreased high-density lipoproteins. As already mentioned in this article, hyperlipidemia has been associated with DR. The ETDRS conducted a retrospective analysis that examined the relationship between serum lipid levels, the presence of retinal hard exudates, and visual acuity in patients with DR. Data from the ETDRS demonstrated that elevated serum lipid levels were associated with an increased risk of retinal hard

<table>
<thead>
<tr>
<th>Table 2. Summary of Selected UKPDS Data*</th>
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<tbody>
<tr>
<td><strong>Question Addressed</strong></td>
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<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Is intensive glycemic control effective in reducing the risk of microvascular complications in type 2 diabetes?</td>
</tr>
<tr>
<td>Does intensive glycemic control reduce the risk of developing ophthalmic clinical and surrogate endpoints in type 2 diabetes?</td>
</tr>
</tbody>
</table>

* \(n = 3867\).

†Progression of retinopathy: 2-step change in modified Early Treatment Diabetic Retinopathy Study retinopathy grade evaluated using stereo retinal photography.

DR = diabetic retinopathy; UKPDS = United Kingdom Prospective Diabetes Study.

exudates in persons with DR. Furthermore, patients with hard exudates were at a 2-fold risk of decreased visual acuity. These findings suggest that lipid lowering may decrease the risk of hard exudate formation and the associated vision loss in patients with DR.

**Diabetic Retinopathy and Pregnancy**

Pregnant women represent an important subset of patients with diabetes and DR. Pregnancy is yet another risk factor for rapid DR progression, and most major medical centers now have high-risk pregnancy programs in which pregnant women with diabetes can obtain appropriate ophthalmic care. Another common problem in this subset of patients is macular edema. Whether this is secondary to fluid retention or metabolic changes that occur during pregnancy remains unclear. A rapid progression of proliferative disease can be seen in patients who have even a minimal degree of retinopathy, thus close follow-up is necessary.

**Compliance with Diabetic Retinopathy Screening**

Screening is an important method by which ophthalmologists may impact the ocular health of their patients with diabetes. Appropriately timed photocoagulation can reduce visual loss by up to 90%; however, despite the importance of monitoring DR, studies suggest that between 30% and 50% of patients do not receive adequate screening because of perceived inconvenience, limited access, and concerns over cost. This disconnect has led many institutions and individuals to examine the feasibility of large population-based screening, and several screening systems have been evaluated.

The gold standard for detection and classification of DR is stereoscopic color fundus photography in 7 standard fields, as defined by the ETDRS. Although it is highly accurate and reproducible, stereoscopic color fundus photography is also labor intensive, and the turnaround time from data acquisition to data interpretation can take weeks, making the technique less than ideal. Mydriatic and nonmydriatic digital systems are alternatives to stereoscopic color fundus photography. Several studies have indicated the superiority of mydriatic over nonmydriatic photography in sensitivity and specificity; however, concern remains as to whether patients will be deterred from mydriasis because dilation is required. Despite its diminished sensitivity, nonmydriatic photography may become an acceptable screening procedure if patients are willing to comply.

Although screening for DR is essential to the ocular health of patients with diabetes, the available screening methods are not substitutes for comprehensive ophthalmic examinations, which are imperative to the diagnosis of other treatable eye diseases, including cataracts and glaucoma. Unfortunately, ocular examination is examiner-dependent, and several studies have indicated that primary care practitioners may overlook clinically important DR. Although available screening options are highly sensitive and highly specific in a research environment, they are technique-dependent and may not be applicable in large patient populations. Additionally, several concerns regarding DR screening reimbursement remain unanswered.

Because of the relationship between DR and systemic factors, such as glycemic control, hypertension, and dyslipidemia, ophthalmologists must take a proactive role not only in their patients' ocular health but also in their overall health. By educating patients on their metabolic status, they will be encouraged to be proactive in the management of their diabetes, which will in turn have a positive impact on the severity and progression of their DR.

**REFERENCES**


