Diabetic Retinopathy

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D iabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years. During the first two decades of disease, nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes have retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of younger-onset patients (type 1 diabetes) and 1.6% of older-onset patients (type 2 diabetes) were legally blind. In the younger-onset group, 86% of blindness was attributable to diabetic retinopathy. In the older-onset group, in which other eye diseases were common, one-third of the cases of legal blindness were due to diabetic retinopathy.

NATURAL HISTORY OF DIABETIC RETINOPATHY

Diabetic retinopathy progresses from mild nonproliferative abnormalities, characterized by increased vascular permeability, to moderate and severe nonproliferative diabetic retinopathy (NPDR), characterized by vascular closure, to proliferative diabetic retinopathy (PDR), characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. Macular edema, characterized by retinal thickening from leaky blood vessels, can develop at all stages of retinopathy. Pregnancy, puberty, blood glucose control, hypertension, and cataract surgery can accelerate these changes.

Vision-threatening retinopathy is rare in type 1 diabetic patients in the first 3–5 years of diabetes or before puberty. During the next two decades, nearly all type 1 diabetic patients develop retinopathy. Up to 21% of patients with type 2 diabetes have retinopathy at the time of first diagnosis of diabetes, and most develop some degree of retinopathy over time. Vision loss due to diabetic retinopathy results from several mechanisms. Central vision may be impaired by macular edema or capillary nonperfusion. New blood vessels of PDR and contraction of the accompanying fibrous tissue can distort the retina and lead to tractional retinal detachment, producing severe and often irreversible vision loss. In addition, the new blood vessels may bleed, adding the further complication of preretinal or vitreous hemorrhage. Finally, neovascular glaucoma associated with PDR can be a cause of visual loss.

RISK FACTORS AND TREATMENTS

Duration of disease

The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. Among younger-onset patients with diabetes in the WESDR, the prevalence of any retinopathy was 8% at 3 years, 25% at 5 years, 60% at 10 years, and 80% at 15 years. The prevalence of PDR was 0% at 3 years and increased to 25% at 15 years (1). The incidence of retinopathy also increased with increasing duration. The 4-year incidence of developing proliferative retinopathy in the WESDR younger-onset group increased from 0% during the first 5 years to 27.9% during years 13–14 of diabetes. After 15 years, the incidence of developing PDR remained stable.

GLYCEMIC CONTROL

The Diabetes Control and Complications Trial (DCCT) investigated the effect of hyperglycemia in type 1 diabetic patients, as well as the incidence of diabetic retinopathy, nephropathy, and neuropathy. A total of 1,441 patients who had either no retinopathy at baseline (primary prevention cohort) or minimal-to-moderate NPDR (secondary progression cohort) were treated by either conventional treatment (one or two daily injections of insulin) or intensive diabetes management with three or more daily insulin injections or a continuous subcutaneous insulin infusion. In the primary prevention cohort, the cumulative incidence of progression in retinopathy over the first 36 months was quite similar between the two groups. After that time, there was a persistent decrease in the intensive group. Intensive therapy reduced the mean risk of retinopathy by 76% (95% CI 62–85). In the secondary intervention cohort, the intensive group had a higher cumulative incidence of sustained progression during the first year. However, by 36 months, the intensive group had lower risks of progression. Intensive therapy reduced the risk of progression by 54% (95% CI 39–66).

The protective effect of glycemic control has also been for confirmed patients with type 2 diabetes. The U.K. Prospective Diabetes Study (UKPDS) demonstrated that improved blood glucose control reduced the risk of developing retinopathy and nephropathy and possibly reduces neuropathy. The overall rate of microvascular complications was decreased by 25% in patients receiving intensive therapy versus conventional therapy. Epidemiological analysis of the UKPDS data showed a continuous relationship between the risk of microvascular complications and glycemia, such that for every percentage point decrease in HbA_{1c} (e.g., from 8 to 7%), there was a 35% reduction in the risk of microvascular complications.

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BLOOD PRESSURE CONTROL

The UKPDS also investigated the influence of tight blood pressure control (2). A total of 1,148 hypertensive patients with type 2 diabetes were randomized to less tight (<180/105 mmHg) and tight blood pressure control (<150/85 mmHg) with the use of an ACE inhibitor or a β-blocker. With a median follow-up of 8.4 years, patients assigned to tight control had a 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual acuity of three lines in association with a 10/5 mmHg reduction in blood pressure. In addition, there were reductions in deaths related to diabetes and strokes.

To determine whether intensive blood pressure control offers additional benefit over moderate control, the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial (3) randomized patients to either intensive or moderate blood pressure control. Hypertensive subjects, defined as having a baseline diastolic blood pressure of ≥90 mmHg, were randomized to intensive blood pressure control (diastolic blood pressure goal of 75 mmHg) versus moderate blood pressure control (diastolic blood pressure goal of 80–89 mmHg). A total of 470 patients were randomized to either nisoldipine or enalapril and followed for a mean of 5.3 years. The mean blood pressure achieved was 132/78 mmHg in the intensive group and 138/86 mmHg in the moderate control group. Although intensive therapy demonstrated a lower incidence of deaths (5.5 vs. 10.7%, $P = 0.037$), there was no difference between the intensive and moderate groups with regard to the progression of diabetic retinopathy and neuropathy.

To determine whether inhibitors of ACE can slow progression of nephropathy in patients without hypertension, the EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID) study group investigated the effect of lisinopril on retinopathy in type 1 diabetes. Eligible patients were not hypertensive, and were normoalbuminuric (85%) or microalbuminuric. The proportion of patients with retinopathy at baseline was similar, but patients assigned to lisinopril had significantly lower HbA_{1c} at baseline. Treatment reduced the development of retinopathy, but the effect may have been due to its pressure-lowering effect in patients who had undetected hypertension. Until these issues are addressed, these findings need to be confirmed before changes to clinical practice can be advocated.

ASPIRIN TREATMENT

The Early Treatment Diabetic Retinopathy Study (ETDRS) investigated whether aspirin (650 mg/day) could retard the progression of retinopathy. After examining progression of retinopathy, development of vitreous hemorrhage, or duration of vitreous hemorrhage, aspirin was shown to have no effect on retinopathy. With these findings, there are no ocular contraindications to the use of aspirin when required for cardiovascular disease or other medical indications.

LASER PHOTOCOAGULATION

The Diabetic Retinopathy Study (DRS) investigated whether scatter (panretinal) photocoagulation, compared with indefinite deferral, could reduce the risk of vision loss from PDR. After only 2 years, photocoagulation was shown to significantly reduce severe visual loss (i.e., best acuity of 5/200 or worse). The benefit persisted through the entire duration of follow-up and was greatest among patients whose eyes had high-risk characteristics (HRCs; disc neovascularization or vitreous hemorrhage with any retinal neovascariztion). The treatment effect was much smaller for eyes that did not have HRCs.

To determine the timing of photocoagulation, the ETDRS examined the effect of treating eyes with mild NPDR to early PDR. The rates of visual loss were low with either treatment applied early or delayed until development of HRCs. Because of this low rate and the risk of complications, the report suggested that scatter photocoagulation be deferred in eyes with mild-to-moderate NPDR. The ETDRS also demonstrated the effectiveness of focal photocoagulation in eyes with macular edema. In patients with clinically significant macular edema, 24% of untreated eyes, compared with 12% of treated eyes, developed doubling of visual angle.

EVALUATION OF DIABETIC RETINOPATHY

An important cause of blindness, diabetic retinopathy has few visual or ophthalmic symptoms until visual loss develops. At present, laser photocoagulation for diabetic retinopathy is effective at slowing the progression of retinopathy and reducing visual loss, but the treatment usually does not restore lost vision. Because these treatments are aimed at preventing vision loss and retinopathy can be asymptomatic, it is important to identify and treat patients early in the disease. To achieve this goal, patients with diabetes should be routinely evaluated to detect treatable disease.

Dilated indirect ophthalmoscopy coupled with biomicroscopy and seven–standard field stereoscopic 30° fundus photography are both accepted methods for examining diabetic retinopathy. Stereo fundus photography is more sensitive at detecting retinopathy than clinical examination, but clinical examination is superior for detecting retinal thickening from macular edema and for early neovascularization. Fundus photography also requires both a trained photographer and a trained reader.

The use of film and digital non-mydriatic images to examine for diabetic retinopathy has been described. Although they permit undilated photographic retinopathy screening, these techniques have not been fully evaluated. The use of the nonmydriatic camera for follow-up of patients with diabetes in the physician's office might be considered in situations where dilated eye examination cannot be obtained.

Guidelines for the frequency of dilated eye examinations have been largely based on the severity of the retinopathy (1,4). For patients with moderate-to-severe NPDR, frequent eye examinations are necessary to determine when to initiate treatment. However, for patients without retinopathy or with only few microaneurysms, the need for annual dilated eye examinations is not as well defined. For these patients, the annual incidence of progression to either proliferative retinopathy or macular edema is low; therefore, some have suggested a longer interval between examinations (5). Recently, analyses suggested that annual examination for some patients with type 2 diabetes may not be cost-effective and that consideration should be given to increasing the screening interval (6). However, these analyses may not have completely considered all the factors: *1*) The analyses assumed that legal blindness

Table 1—*Ophthalmologic examination schedule*

Patient group	Recommended first examination	Minimum routine follow-up*
Type 1 diabetes	Within 3–5 years after diagnosis of diabetes once patient is age 10 years or older†	Yearly
Type 2 diabetes	At time of diagnosis of diabetes	Yearly
Pregnancy in preexisting diabetes	Prior to conception and during first trimester	Physician discretion pending results of first trimester exam

*Abnormal findings necessitate more frequent follow-up. †Some evidence suggests that the prepubertal duration of diabetes may be important in the development of microvascular complications; therefore, clinical judgment should be used when applying these recommendations to individual patients.

was the only level of visual loss with economic consequences, but other visual function outcomes, such as visual acuity worse than 20/40, are clinically important, occur much more frequently, and have economic consequences. 2) The analyses used NPDR progression figures from newly diagnosed patients with diabetes (7). Although rates of progression are stratified by HbA$_{1c}$ levels, newly diagnosed patients are different from those with the same level of retinopathy and have a longer diabetes duration. While rates of progression correlate with HbA$_{1c}$ levels, newly diagnosed patients with the same level of retinopathy progress differently than those with longer duration of disease. A person with a longer duration of diabetes is more likely to progress during the next year of observation (8). 3) The rates of progression were derived from diabetic individuals of northern European extraction and are not applicable to other ethnic and racial groups who have higher rates of retinopathy progression, such as African- and Hispanic-Americans (9,10).

In determining the examination interval for an individual patient, the eye care provider should also consider the implications of less frequent eye examinations. Older people are at higher risk for cataract, glaucoma, age-related macular degeneration, and other potentially blinding disorders. Detection of these problems adds value to the examination but is rarely considered in analyses of screening interval. Patient education also occurs during examinations. Patients know the importance of controlling their blood glucose, blood pressure, and serum lipids, and this importance can be reinforced at a time when patients are particularly aware of the implications of vision loss. In addition, long intervals between follow-up visits may lead to difficulties in maintaining contact with patients. Patients may be

unlikely to remember that they need an eye examination after several years have passed.

After considering these issues, and in the absence of empirical data showing otherwise, persons with diabetes should have an annual eye examination.

SUMMARY AND RECOMMENDATIONS

Treatment modalities exist that can prevent or delay the onset of diabetic retinopathy, as well as prevent loss of vision, in a large proportion of patients with diabetes. The DCCT and the UKPDS established that glycemic and blood pressure control can prevent and delay the progression of diabetic retinopathy in patients with diabetes. Timely laser photocoagulation therapy can also prevent loss of vision in a large proportion of patients with severe NPDR and PDR and/or macular edema. Because a significant number of patients with vision-threatening disease may not have symptoms, ongoing evaluation for retinopathy is a valuable and required strategy.

The recommendations for initial and subsequent ophthalmologic evaluation of patients with diabetes are stated below and summarized in Table 1.

GUIDELINES

- Patients with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 3–5 years after the onset of diabetes. In general, evaluation for diabetic eye disease is not necessary before 10 years of age. However, some evidence suggests that the prepubertal duration of diabetes may be important in the development of microvascular complications; therefore, clinical judgment should be used when

applying these recommendations to individual patients. (B)
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after diabetes diagnosis. (B)
- Subsequent examinations for both type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing the presence of diabetic retinopathy and is aware of its management. Examinations will be required more frequently if retinopathy is progressing. This follow-up interval is recommended recognizing that there are limited data addressing this issue. (B)
- When planning pregnancy, women with preexisting diabetes should have a comprehensive eye examination and should be counseled on the risk of development and/or progression of diabetic retinopathy. Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and close follow-up throughout pregnancy (Table 1). This guideline does not apply to women who develop gestational diabetes, because such individuals are not at increased risk for diabetic retinopathy. (B)
- Patients with any level of macular edema, severe NPDR, or any PDR require the prompt care of an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. Referral to an ophthalmologist should not be delayed until PDR has developed in patients who are known to have severe nonproliferative or more advanced retinopathy. Early referral to an ophthalmologist is particularly important for patients with type 2 diabetes and severe

NPDR, since laser treatment at this stage is associated with a 50% reduction in the risk of severe visual loss and vitrectomy. (E)

- Patients who experience vision loss from diabetes should be encouraged to pursue visual rehabilitation with an ophthalmologist or optometrist who is trained or experienced in low-vision care. (E)

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