POSITION STATEMENT

Diabetic Retinopathy

AMERICAN DIABETES ASSOCIATION

Originally approved November 1997. Most recent review/revision, 1998.

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SCREENING FOR DIABETIC RETINOPATHY

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes. The prevalence of retinopathy is strongly related to the duration of diabetes. After 20 years of diabetes, nearly all patients with type 1 diabetes and >60% of patients with type 2 diabetes have some degree of retinopathy. Diabetic retinopathy poses a serious threat to vision. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of younger-onset patients (aged <30 years at diagnosis, an operational definition of type 1 diabetes) and 1.6% of older-onset patients (aged ≥30 years at diagnosis, an operational definition of type 2 diabetes) were legally blind. In the younger-onset group, 86% of blindness was attributable to diabetic retinopathy. In the older-onset group, where other eye diseases were common, one-third of the cases of legal blindness were due to diabetic retinopathy. Overall, diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults aged 20–74 years.

The recommendations in this paper are based on the technical review on the subject,[1] which should be consulted for further information.

NATURAL HISTORY OF DIABETIC RETINOPATHY

Screening strategies depend on the rates of appearance and progression of diabetic retinopathy and on risk factors that alter these rates. Vision-threatening retinopathy virtually never appears in type 1 patients in the first 3–5 years of diabetes or before puberty. Over the subsequent 2 decades, nearly all type 1 patients develop retinopathy. Up to 21% of patients with type 2 diabetes have recently been found to have retinopathy at the time of first diagnosis of diabetes, and most develop some degree of retinopathy over subsequent decades.

In general, the progression of retinopathy is orderly, advancing 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. Pregnancy, puberty, and cataract surgery can accelerate these changes.

Vision loss due to diabetic retinopathy results from several mechanisms. First, central vision may be impaired by macular edema or capillary nonperfusion. Second, the 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. Third, the new blood vessels may bleed, adding the further complication of preretinal or vitreous hemorrhage.

There are several epidemiological studies describing the onset and progression of diabetic retinopathy. The WESDR can serve as a representative model. The WESDR attempted to identify all diabetic patients treated by physicians in an 11-county area in southern Wisconsin. Between 1979 and 1980, 1,210 patients with younger-onset diabetes and 1,780 patients with older-onset diabetes were entered into the study. Patients had several clinical assessments, including seven-field stereo fundus photographs and measurement of glycated hemoglobin. A 4-year follow-up examination repeated the fundus photographs. The WESDR found the relationship described above between onset of retinopathy and duration of diabetes. It also established that progression of retinopathy was a function of baseline retinopathy. The more severe the baseline retinopathy, the greater the frequency of progression to vision-threatening retinopathy. Conversely, among type 2 diabetic patients whose baseline photographs showed no retinopathy, there was less PDR or progression to severe macular edema over 4 years. The WESDR epidemiological data were limited primarily to white northern European extraction populations and may not be applicable to African-American, Hispanic-American, or Asian-American populations or to others with a high prevalence of diabetes and retinopathy.

There has been extensive research on potential risk factors for retinopathy. There is now a large and consistent set of observational studies documenting the association of poor glucose control and retinopathy.

In the Diabetes Control and Complications Trial (DCCT), a definitive relationship was demonstrated in type 1 diabetes between hyperglycemia and diabetic microvascular complications,

including retinopathy, nephropathy, and neuropathy. A group of 1,441 patients with type 1 diabetes who had either no retinopathy at baseline (primary prevention cohort) or with minimal-to-moderate NPDR (secondary progression cohort) were treated by either conventional therapy or intensive diabetes management with three or more daily insulin injections or a continuous subcutaneous insulin infusion. In contrast, conventional therapy included one or two daily injections of insulin. The patients were followed for 4–9 years with seven-field stereoscopic photography every 6 months. The DCCT showed that intensive insulin therapy reduced or prevented the development of retinopathy by 27% as compared with conventional therapy. In addition, intensive therapy reduced the progression of diabetic retinopathy by 34–76%. Early treatment with intensive therapy was most effective. However, intensive therapy had a substantial beneficial effect over the entire range of retinopathy. This improvement was achieved with an average 10% reduction in HbA_{1c} from 8 to 7.2%.

The largest and longest study on patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS), conclusively demonstrated that improved blood glucose control in these patients reduces the risk of developing retinopathy and nephropathy and possibly reduces neuropathy. The overall microvascular complications rate 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., 9 to 8%), there was a 35% reduction in the risk of microvascular complications.

The results of the DCCT and UKPDS showed that while intensive therapy does not prevent retinopathy completely, it reduces the risk of the development and progression of diabetic retinopathy. This

can be translated clinically to a preservation of eyesight and reduced need for laser treatment.

It also seems clear that proteinuria is associated with retinopathy. High blood pressure is an established risk factor for the development of macular edema and is associated with the presence of PDR. Observations indicate an association of serum lipid levels with lipid in the retina (hard exudates) and visual loss. Thus, systemic control of blood pressure and serum lipids may be important in the management of diabetic retinopathy. In addition, several case series and a controlled prospective study suggest that pregnancy in type 1 diabetic patients may aggravate retinopathy.

EFFICACY OF LASER PHOTOCO-AGULATION SURGERY

One of the main motivations for screening for diabetic retinopathy is the established efficacy of laser photocoagulation surgery in preventing visual loss. Two large National Institutes of Health–sponsored trials, the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), provide the strongest support for the therapeutic benefit of photocoagulation surgery.

The DRS tested whether scatter (panretinal) photocoagulation surgery could reduce the risk of vision loss from PDR. There were 1,758 participating patients. By the 2-year analysis, a dramatic benefit of photocoagulation surgery was evident. Severe visual loss (i.e., best acuity of 5/200 or worse) was seen in 15.9% of untreated eyes versus 6.4% of treated eyes. The benefit was greatest among patients whose baseline evaluation revealed high-risk characteristics (HRCs) (chiefly disc neovascularization or vitreous hemorrhage with any retinal neovascularization). Of control eyes with HRC, 26% progressed to severe visual loss versus 11% of treated eyes. The absolute benefit of photocoagulation surgery was much smaller for

eyes that did not have HRC. Given the risk of a modest loss of visual acuity and of contraction of visual field from panretinal laser surgery, such therapy has been primarily recommended for eyes approaching or reaching HRCs.

ETDRS assessed the value of argon laser surgery and aspirin in early PDR, moderate-to-severe NPDR, and diabetic macular edema (a complication seen in the presence of both PDR and NPDR). The ETDRS established the benefit of focal laser photocoagulation surgery in eyes with macular edema, particularly those with clinically significant macular edema. In the part of the ETDRS that studied macular edema, 1,490 eyes with macular edema were randomized to deferral of photocoagulation surgery (until PDR with HRC occurred) and 754 eyes were randomized to immediate focal photocoagulation surgery. In patients with clinically significant macular edema after 2 years, 20% of untreated eyes had a doubling of the visual angle (e.g., 20/50 to 20/100) compared with 8% of treated eyes. In other results from the ETDRS, aspirin did not prevent the development of high-risk PDR and did not reduce the risk of visual loss, nor increase the risk of vitreous hemorrhage. The relative risk of vitreous or preretinal hemorrhage for patients assigned to aspirin compared with patients assigned to placebo in eyes that had new vessels definitely present at baseline was 1.05 (99% CI [0.81–1.36]). This included patients in the deferral group who in follow-up had scatter laser photocoagulation surgery on reaching HRC. These findings suggest there are no ocular contraindications to aspirin when required for cardiovascular disease or other medical indications.

Other results from the ETDRS indicate that, provided careful follow-up can be maintained, scatter photocoagulation surgery is not recommended for eyes with mild or moderate NPDR. When retinopathy is more severe, scatter photocoagulation surgery should be considered, and usually should not be delayed,

if the eye has reached the high-risk proliferative stage. In older-onset patients with severe NPDR or less than high-risk PDR, the risk of severe visual loss and vitrectomy is reduced ~50% by laser photocoagulation surgery at these earlier stages.

Laser photocoagulation surgery in both the DRS and the ETDRS was beneficial in reducing the risk of further visual loss, but generally not beneficial in reversing already diminished acuity. This preventive effect and the fact that patients with PDR or macular edema may be asymptomatic provide strong support for a screening program to detect diabetic retinopathy.

COST-EFFECTIVENESS OF SCREENING FOR RETINOPATHY

There have been several cost-effectiveness analyses of screening for diabetic retinopathy. The currently published analyses have assessed semiannual, annual, and biennial screening programs. Although the modeling techniques and the component costs have differed substantially, the basic message of all these analyses is the same. Screening for diabetic retinopathy saves vision at a relatively low cost, and even this cost is often less than the disability payments provided to people who would go blind in the absence of a screening program.

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 intensive diabetes management to obtain near-euglycemic 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. Since some patients with vision-threatening pathologies may not have symptoms, ongoing evaluation for retinopathy is a valuable and required strategy.

Dilated ETDRS seven–standard field stereoscopic 30° fundus photography is more sensitive at detecting retinopathy than is clinical examination, although clinical examination is often superior for detecting retinal thickening associated with macular edema and may be better at identifying fine caliber neovascularization of the optic disk or elsewhere in the retina. Proper fundus photographs require a photographer skilled in obtaining the rigorously defined and technically challenging ETDRS photographic fields of appropriate quality and a reader skilled in the interpretation of the photographs. If either of these components is not available or do not meet the defined standards, then they cannot be substituted for a dilated ophthalmic examination by an eye care provider with experience in the management of diabetic retinopathy, even for screening purposes.

Recent techniques permit the acquisition of high-quality photographs through undilated pupils and the acquisition of images in digital format. Although this may eventually permit undilated photographic retinopathy screening, no rigorous studies to date validate the equivalence of these photographs with seven–standard field stereoscopic 30° fundus photography for assessing diabetic retinopathy. The use of the nonmydriatic camera for follow-up of patients with diabetes in the physician's office might be considered only in situations where dilated eye examination cannot be obtained. However, at this time, these technologies are not considered a replacement for dilated seven– standard field stereoscopic fundus photography or for eye examinations by an experienced ophthalmologist or optometrist for the screening, diagnosis, grading, or treatment of diabetic retinopathy.

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

GUIDELINES

1. Patients ≥10 years of age 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, screening for diabetic eye disease is not necessary before 10 years of age. However, some evidence suggests that the prepubertal duration of

Table 2. Opthalmologic examination schedule

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

*Abnormal findings necessitate more frequent follow-up. †As indicated in WESDR, these are operational definitions of type 1 and type 2 diabetes based on age (age <30 years at diagnosis, type 1, age ≥30 years at diagnosis, type 2) and not pathogenetic classification. For detailed information, see the "Diabetic retinopathy" technical review (*Diabetes Care* 21:143–159, 1998). ‡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.

diabetes may be important in the development of microvascular complications; therefore, clinical judgment should be used when applying these recommendations to individual patients. Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes is made.

2. 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. As previously discussed, data from WESDR showed that patients with type 2 diabetes who received ETDRS standard seven-field stereoscopic color fundus photographs that revealed no retinopathy when evaluated by a skilled reader did not generally require another retinopathy examination for 4 years because of low risk of disease progression. However, in patients with gross proteinuria or poor glycemic control (>2 SD from the mean of the nondiabetic population), annual examinations were indicated even if the initial review using fundus photography revealed no retinopathy.

Despite the WESDR findings, we believe that an annual eye examination is still warranted for the following reasons. First, these data were derived from a study that evaluated white, northern European–extraction patients with diabetes living in southern Wisconsin. The results may not be applicable to African-American, Hispanic-American, Asian-American, or other populations where it is unknown if retinopathy progresses in the same manner. Second, a well-designed quality-control program was used in WESDR to ensure accurate interpretation of fundus photographs. Such quality control efforts have not been standardized or completely described, let alone adopted nationwide. Third, the potential for patient loss to follow-up induced by an extended hiatus between ophthalmic evaluations introduces further uncertainty.

3. 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 1st 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.

4. 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.

5. 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.

REFERENCE

1. Aiello LP, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL, Klein R: Diabetic retinopathy (Technical Review). *Diabetes Care* 21:143–156, 1998