A team approach, which involves primary care physicians, endocrinologists, ophthalmologists, nurses, optometrists, nutritionists, and dietitians, is of primary importance for identifying and treating diabetic retinopathy, the retinal complication of diabetes mellitus. This article describes various ocular signs of diabetic retinopathy, such as microaneurysms, hard exudates, intraretinal hemorrhages, and cotton wool spots, all of which are visible on direct ophthalmoscopy and should trigger prompt consultation with an ophthalmologist. Referral of patients with diabetes to ophthalmologists for regular dilated eye examinations also is vital, as timely treatment can preserve vision in many patients. Additional ways in which physicians can help control or prevent progression of diabetic retinopathy include strict control of blood glucose, body weight, cholesterol, and blood pressure. A team approach to prevention and diagnosis gives patients with diabetes the best opportunity to preserve their vision.

Diabetic Retinopathy: An Overview for Non-Ophthalmologists
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ABSTRACT
Nearly all patients with type 1 diabetes, and most with type 2 diabetes, eventually develop diabetic eye diseases, including diabetic retinopathy. Even in the advanced stages, diabetic retinopathy can be asymptomatic; yet it is the leading cause of new cases of blindness among working-age US adults. This article describes various ocular signs of diabetic retinopathy, such as microaneurysms, hard exudates, intraretinal hemorrhages, and cotton wool spots, all of which are visible on direct ophthalmoscopy and should trigger prompt consultation with an ophthalmologist. Referral of patients with diabetes to ophthalmologists for regular dilated eye examinations also is vital, as timely treatment can preserve vision in many patients. Additional ways in which physicians can help control or prevent progression of diabetic retinopathy include strict control of blood glucose, body weight, cholesterol, and blood pressure. A team approach to prevention and diagnosis gives patients with diabetes the best opportunity to preserve their vision.

Epidemiology
Diabetes is a common disease. In 1997, an estimated 124 million people worldwide were affected with diabetes; 97% of those had type 2 diabetes. The World Health Organization estimates that by 2025, 300 million adults worldwide will have type 1 or type 2 diabetes. In the United States alone, more than 16 million people are affected; yet the incidence of diabetes is expected to increase, presaged by high rates of impaired fasting glucose levels, high rates of obesity, and the trend toward a sedentary lifestyle. Diabetes is particularly prevalent in US...
minority populations, such as African Americans, Mexican Americans, and Native Americans.\(^3\)

The life expectancy of patients with diabetes is 10 to 15 years shorter than that of individuals who do not have the disease. On average, patients with diabetes are 3 times more likely to be hospitalized compared with patients without diabetes.\(^3\) In 1996, the direct cost of healthcare associated with diabetes in the United States was $120 million, a large portion of which was used for treatment of patients with complications.\(^3\) The expense skyrockets when “indirect” costs are included (eg, costs of caregiver services provided by family members, as well as patients’ and caregivers’ loss of productivity). One study reported that diabetes cost $98 billion in the United States in 1997.\(^4\)

Retinal complications develop in 50% of all Americans with diabetes.\(^1\) Early all patients with type 1 diabetes will develop retinopathy within 20 years of diabetes diagnosis, although vision-threatening changes are rare in the first 3 to 5 years after diagnosis or before puberty.\(^6\) Among patients with type 2 diabetes, up to 20% will have retinopathy at the time of the diabetes diagnosis, and more than 60% will develop some degree of retinopathy within 20 years.\(^6\) Diabetic retinopathy is thought to be the leading cause of new cases of blindness among adults aged 20 to 74 years.\(^6\)

CLINICAL PRESENTATION AND NATURAL HISTORY

Diabetic retinopathy is classified into 2 main stages according to how advanced the disease has become. The first stage is nonproliferative diabetic retinopathy (NPDR), which can be further subclassified as mild, moderate, severe, or very severe, depending on clinical examination findings. NPDR may progress to the second stage, proliferative diabetic retinopathy (PDR), which is characterized by the growth of new blood vessels on the surface of the retina and/or optic disc that can extend into the vitreous. PDR can be subclassified into non–high-risk and high-risk categories.

NONPROLIFERATIVE DIABETIC RETINOPATHY

The hallmarks of NPDR, which can be seen with direct ophthalmoscopy, are microaneurysms, cotton wool spots, hard exudates, retinal hemorrhages, venous beading (Figure 1, arrows), and intraretinal microvascular abnormalities (IRMA) (Figure 1, arrowheads). Patients may not have visual symptoms; they may be asymptomatic despite the presence of all of the signs at examination.

Diabetic macular edema, a sign that may be present at any stage of diabetes, is the most common cause of vision loss in patients with diabetic retinopathy (Figure 2). The macula is the central part of the retina that provides central vision and permits visualization of details. In macular edema, damaged blood vessels leak fluid into the macula. At times, the leakage is associated with lipid deposition. The abnormal accumulation of fluid within the retina causes the macula to swell, resulting in blurred vision. In contrast, macular capillary nonperfusion, or macular ischemia, also may lead to impaired central vision in some patients.

**Figure 1. Ocular Signs Associated with Nonproliferative Diabetic Retinopathy**

Fundus photograph showing various ocular signs associated with nonproliferative diabetic retinopathy, including dilatations of retinal veins called venous beading (shown by the arrows) and intraretinal microvascular abnormalities, IRMA (shown by arrowheads).

Source: American Academy of Ophthalmology.

**Figure 2. Normal Appearance (A) and Diabetic Macular Edema with Vascular Leakage, Fluid, and Exudates in the Macula (B)**

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patients who have had diabetes for fewer than 5 years, the prevalence of macular edema is 5%, but among those who have had diabetes for more than 15 years, the prevalence can be as high as 15%. The presence of cotton wool spots is another ocular sign that can be seen with a direct ophthalmoscope through a nondilated pupil (Figure 3). These spots are superficial white lesions with feathery edges that represent ischemia or infarction of the nerve-fiber layer of the retina.

Proliferative Diabetic Retinopathy

PDR is the more severe stage of diabetic eye disease and the major cause of severe loss of vision and blindness due to diabetic retinopathy. PDR can be asymptomatic. Therefore, it is vitally important for primary care physicians to monitor patients with diabetes and refer them for ophthalmologic consultation and treatment if necessary before vision loss occurs.

Among patients with diabetes who received a diagnosis before age 30 years and who take insulin, the prevalence of PDR 5 years postdiagnosis is rather low. However, by 15 years after diagnosis, the prevalence is greater than 20%, and by 20 years prevalence increases substantially to greater than 50%. For patients who receive a diagnosis when they are 30 years or older, the prevalence of PDR is lower. By 20 years after diagnosis, the prevalence of PDR among these patients is as high as 20%. Therefore, 1 in 5 patients is at risk for developing severe vision loss.

In PDR, the leading theories of pathogenesis focus on ischemia and increased levels of serum glucose, which may result in increased production of vascular endothelial growth factor (VEGF). High levels of growth factors, particularly of VEGF, precede the development of new vessels, which are the hallmark of PDR (Figure 4). Neovascularization consists of new, abnormal blood vessels that are fragile and bleed frequently. These new blood vessels can form over the optic disc (neovascularization of the disc [NVD]; Figure 4A) or on the retina (neovascularization elsewhere [NVE]; Figure 4B). Bleeding from neovascularization can result in severe vision loss due to preretinal (Figure 5), retinal, or vitreous hemorrhage. Patients with vitreous hemorrhage may have many floaters or sudden and severe vision loss.

In addition, fibrovascular tissue often accompanies neovascularization. Fibrovascular tissue can contract, leading to distortion, tearing, or tractional detachment of the retina. The resulting vision loss is severe and often irreversible. The size of the NVD and/or NVE (Figure 4), in relation to the diameter of the optic disc, and the presence or absence of vitreous hemorrhage are used to determine if the PDR is high-risk, thereby requiring prompt laser treatment. Although some changes may be irreversible, the goal of treatment for PDR is to alleviate neovascularization and prevent vision loss. In some cases, such as in patients with vitreous hemorrhage, vision may be improved with surgery to remove the blood.

Neovascularization also may occur on the iris, a condition referred to as rubeosis iridis (Figure 6). Neovascularization of the iris also can be associated with neovascularization of the angle; if extensive, such neovascularization may result in angle closure glaucoma.

Figure 3. Cotton Wool Spot

Fundus photograph showing presence of cotton wool spot, an ocular sign often seen in nonproliferative diabetic retinopathy.

Figure 4. Signs of Proliferative Diabetic Retinopathy with Neovascularization of the Disc (A) and Neovascularization Elsewhere (B)
closure glaucoma. Patients with acute angle-closure glaucoma may present with a painful, red eye that is associated with high intraocular pressure, nausea, and vomiting. Immediate treatment to lower intraocular pressure and laser photoagulation of the retina to decrease or obliterate the neovascularization are necessary to salvage vision.

THE EFFECT OF SYSTEMIC CONDITIONS ON DIABETIC RETINOPATHY

Certain systemic diseases and conditions may affect the onset and severity of diabetic retinopathy. Elevated serum lipid levels are associated with the presence and severity of retinal hard exudates in NPDR and diabetic macular edema (DME). Hypertension, especially when poorly controlled over many years, is often associated with a higher risk of progression of DME and diabetic retinopathy. Ocular ischemia, which can occur in asymmetric carotid artery occlusive disease, may worsen the retinopathy. Advanced diabetic renal disease and anemia have also been shown to adversely affect diabetic retinopathy.

Pregnancy is known to worsen diabetic retinopathy. Therefore, it is important that women with diabetes who become pregnant have more frequent retinal evaluations. In general, it is recommended that women be examined before conception or early in the first trimester, and every 3 months thereafter, or at the discretion of the ophthalmologist. Visual loss may occur from NPDR with DME or from the accelerated complications of PDR. Many of these patients may have some regression of retinopathy after delivery. However, if high-risk PDR develops during pregnancy, laser photoagulation treatment is recommended.

STANDARDS OF CARE

GLUCOSE CONTROL

Two major multicenter studies have documented that systemic glucose control is a key factor in preventing diabetic retinopathy and controlling its progression. The Diabetes Control and Complications Trial (DCCT) was conducted in the 1980s and early 1990s and involved more than 1400 patients with type 1 diabetes. Patients were randomized to receive intensive or conventional therapy; those in the intensive-therapy group were then randomized to receive medication via an insulin pump or via at least 3 daily injections. In the group receiving at least 3 daily injections, frequent blood glucose monitoring determined the number of additional injections administered daily, if any. Those in the conventional-therapy group received 1 or 2 daily insulin injections. In patients with no baseline retinopathy, intensive insulin therapy led to a 76% decrease in the mean risk of developing retinopathy during the 4-year to 9-year follow-up period. In patients who already had mild-to-moderate retinopathy at baseline, intensive therapy led to a 54% decrease in the progression of retinopathy. More importantly, it also led to a 47% decrease in the development of severe NPDR or PDR.

Figure 5. Preretinal Hemorrhage

As fragile new vessels grow, they may bleed into the vitreous or on the surface of the retina; the latter is known as preretinal hemorrhage. Source: American Academy of Ophthalmology.

Figure 6. Neovascularization of the Iris (Rubeosis Iridis)

Neovascularization in diabetes is not always confined to the retina. In this photograph, neovascularization of the iris (rubeosis iridis) is seen. Source: American Academy of Ophthalmology.
The DCCT investigators noted that patients with PDR or severe NPDR may be at higher risk for accelerated progression of diabetic retinopathy after the start of intensive therapy; however, the abnormalities often disappeared by 18 months. Patients with early worsening who received intensive therapy ultimately had a 74% reduction in the risk of subsequent progression (P < .001 vs conventional therapy). Thus, the DCCT investigators have recommended striving for glycemic control. Patients should be closely observed by their ophthalmologists in order to monitor and treat any necessary ocular changes.

In the more recent United Kingdom Prospective Diabetes Study (UKPDS), more than 3800 patients with newly diagnosed type 2 diabetes were followed up for more than 10 years. The average value of glycosylated hemoglobin (HbA1c) was 7.0% in the group receiving intensive glucose control with either a sulfonylurea or insulin. This result was 11% lower than the average HbA1c value (7.9%) in the group receiving diet therapy. In the UKPDS, the group with an average HbA1c value of 7.0% had a 25% lower risk of microvascular complications compared with the group with an average HbA1c value of 7.9%. Therefore, intensive glycemic control has been proven to decrease the risk of microvascular complications, such as retinopathy, neuropathy, and nephropathy.

### Blood Pressure Control

Hypertension is often associated with type 2 diabetes. At age 45 years, approximately 40% of patients with type 2 diabetes are hypertensive, and the proportion increases to 60% by age 75 years. Hypertension increases the risk of cardiovascular disease associated with type 2 diabetes and also is a risk factor for retinopathy and nephropathy. Thus, controlling blood pressure is critical when the goal is preventing or controlling the progression of diabetic retinopathy.

To study how hypertension may contribute to the complications of diabetes, the UKPDS team randomized patients into 2 groups. One group received either a beta blocking agent (atenolol) or an angiotensin-converting enzyme inhibitor (captopril) to maintain strict blood pressure control; the target was below 150/85 mm Hg. The other group had less strictly controlled hypertension, with a target blood pressure of below 180/105 mm Hg. After a median follow-up period of 8.4 years, the group maintaining strict blood pressure control had a 37% reduction in the incidence of microvascular complications, a 32% reduction in diabetes-related deaths, and a 44% reduction in strokes compared with the group with less strictly controlled blood pressure. The group maintaining strict blood pressure control also had a 34% reduction in risk of progression of retinopathy, and a 47% reduced risk of deterioration in visual acuity by 3 lines of the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Therefore, the investigators concluded that controlling blood pressure is essential for slowing the progression of diabetic retinopathy, reducing the other complications of diabetes, and lowering mortality risk.

For the patient with diabetes, careful monitoring of both blood glucose and blood pressure levels are extremely important. The primary care physician and ophthalmologist should be communicating frequently and effectively while developing regimens that help the patient to achieve maximum control of glucose and blood pressure levels. The treatment plan must be individualized for each patient, taking into account his or her systemic and ocular disease and disease progression, level of adherence to therapeutic agents, and tolerance of specific levels of blood pressure and blood glucose.

### Diagnosis

#### Screening by Primary Care Physicians

Numerous studies have been conducted to compare the effectiveness of various screening methods for diabetic retinopathy. Siu et al found that retinal photography, without pharmacologic mydriasis, was significantly more effective than direct ophthalmoscopy for detecting diabetic retinopathy. In a study conducted among 897 patients from the United Kingdom, Ovens and colleagues assessed the ability of general practitioners to detect diabetic retinopathy with direct ophthalmoscopy and by examining retinal images as 35-mm color transparencies. The sensitivity for detecting diabetic retinopathy increased from 62.6% with direct ophthalmoscopy to 79.2% with retinal photographs. Klein et al assessed the concordance among 3 methods of detecting retinopathy and demonstrated a 54.5% agreement between the results of direct ophthalmoscopy and those of grading from stereoscopic photographs taken with the standard 30-degrees camera (through dilated pupils). However, the agreement was 82.5% for grading retinopathy with 45-degrees photographs taken through undilated pupils and 30-degrees photographs taken through dilated pupils.

Yet, in a rural clinic that serves Native Americans with diabetes, Griffith and colleagues compared the accuracy of referrals made based on 2 screening methods — direct ophthalmoscopy.
through undilated pupils performed by trained primary care physicians and 7-view nonstereoscopic, mydriatic fundus photographs read by 2 general ophthalmologists and a retina specialist. Among the 243 examinations performed, the authors found that these screening methods were highly sensitive for referring patients with retinopathy: agreement was 100% with direct ophthalmoscopy performed by primary care physicians, 94% when nonstereoscopic photographs were read by the general ophthalmologist, and 100% when the nonstereoscopic images were read by a retina specialist.

Therefore, in general, retinal photographs taken with a standard fundus camera through dilated pupils or with a nonmydriatic camera, or direct examinations by ophthalmologists and retina specialists are more sensitive for detecting diabetic retinopathy than examinations performed by primary care physicians using direct ophthalmoscopy through undilated pupils. However, careful screening by trained primary care physicians may be a clinically acceptable strategy, especially in areas where ophthalmologists are not readily available.

**Tests Performed by Ophthalmologists**

Ophthalmologists, especially retina specialists, routinely evaluate patients with diabetes for diabetic retinopathy. During the examination, slit-lamp biomicroscopy is used to view the anterior and posterior segments of the eye. Indirect ophthalmoscopy is used to examine the peripheral retina through a dilated pupil. Ophthalmologists look carefully at the retina to detect signs of NPDR (retinal hemorrhages, venous beading, IRMA) or PDR (neovascularization). In addition, contact lens biomicroscopy is commonly used to examine the macula for the presence of edema.

Fundus photographs of the eye are taken frequently to document the stages of diabetic retinopathy (Figure 7A). Photographs of the retina are useful in monitoring retinopathy and guiding treatment. Fluorescein angiography is another useful tool for managing patients with diabetic retinopathy (Figure 7B). Fluorescein angiography involves taking serial pictures of the retina after intravenous injection of fluorescein dye. The dye courses through the systemic circulation and allows visualization of the circulation in the eye. If macular edema is present, fluorescein angiography may reveal leaking microaneurysms surrounding the macula. These abnormal microaneurysms can be treated with focal laser photocoagulation to stop further leakage and the resultant swelling of the retina. In patients with PDR, fluorescein angiography can be useful for identifying neovascularization. Neovascular blood vessels are abnormal and leak profusely during fluorescein angiography. After fluorescein angiography, patients may notice bright yellow- or orange-colored urine, which represents the fluorescein dye leaving their circulation.

The principal method used in treating diabetic retinopathy is laser photocoagulation, which is often an in-office procedure. During the procedure, the fully alert patient sits at a device similar to a slit lamp; a contact lens is placed on the eye, allowing a magnified, stereoscopic view of the retinal area to be treated.
TREATMENT
Depending on the stage of the retinopathy, it can be treated with laser photocoagulation or surgery. Both treatments are effective for preventing further vision loss. In some patients, treatment may even improve vision. Even patients with advanced retinopathy may have a 90% chance of saving their vision if treated before retinal damage is too severe and irreversible.5

LASER PHOTOCOAGULATION
Panretinal laser photocoagulation is the standard treatment for patients with PDR. The procedure is done in the office with the patient alert and sitting at the slit-lamp biomicroscope. The pupil is dilated and topical anesthesia is applied to the eye. Using a laser that is attached to the slit-lamp biomicroscope, the ophthalmologist focuses a beam of laser light through a special handheld contact lens on the cornea, the transparent anterior surface of the eye (Figure 8). The laser is directed in a scatter pattern over the periphery of the retina and is applied at sufficient power to cause whitening of the outer retina (Figure 9). In a patient with high-risk PDR, often 1200 to 1800 laser spots are applied throughout the retina.

The exact mechanism for regression of neovascularization after panretinal laser photocoagulation is unknown. It is known, however, that retinal ischemia due to diabetic microvascular complications leads to excessive stimuli for neovascularization. Application of laser photocoagulation destroys ischemic retinal tissues in the periphery of the retina (Figure 10). One hypothesis is that destruction of abnormal ischemic retinal tissue decreases angiogenic stimulating factors, such as VEGF, and may increase oxygenation of the retina.

Focal laser photocoagulation is used to treat macular edema. After leaking microaneurysms are identified on fluorescein angiography, small laser spots are applied to the microaneurysms to seal them (Figure 11). Closing the abnormal and leaky vessels has been shown to significantly reduce the risk of moderate loss of vision by more than 50%.23

Laser photocoagulation does have potential side effects. The destruction of the peripheral retina may cause decreased night and peripheral vision. During the consent process, patients are informed of both the benefits and potential side effects of laser photocoagulation. Although it is not risk-free, laser photocoagulation is extremely effective for treating PDR and macular edema and is currently the standard of care.

SURGERY
When diabetic retinopathy is complicated by a nonclearing vitreous hemorrhage, rhegmatogenous (a tear in the retina is seen) retinal detachment, or traction on the macula, surgical intervention is indicated. Patients may undergo surgery while under monitored anesthesia care with supplementary retrobulbar anesthesia, or they can be placed under general anesthesia.

Vitrectomy, which is extraction of the vitreous (the collagenous matrix in the posterior segment of the eye), is a common surgical procedure to
remove blood from the vitreous. Vitrectomy can be combined with endolaser photocoagulation (laser photocoagulation applied with a probe inside the eye) and other vitreoretinal microsurgical techniques to treat PDR.

**Investigational Therapy**

Various clinical trials at the Wilmer Eye Institute of the Johns Hopkins University and at other leading eye centers throughout the world are currently investigating the use of corticosteroids to treat DME. The steroids are injected periocularly or intravitreally (triamcinolone), implanted in a biodegradable drug-delivery device (dexamethasone), or implanted in a long-acting device (fluocinolone). Steroidal therapy has been shown to be beneficial in selected patients whose diabetic macular edema has been refractory to standard laser therapy.

In addition, studies are under way to evaluate the role of supplemental oxygen therapy (phase I/II studies are being conducted at the Wilmer Eye Institute), anti-VEGF, and other compounds in the management of DME and retinal neovascularization. In the near future, the results of these ongoing trials may redefine the standard of care for diabetic eye diseases.

**Team Approach to Screening**

In the DCCT and UKPDS trials, teams of ophthalmologists, primary care physicians, diabetologists, and nurses worked together to help patients maintain strict control of blood glucose and blood pressure levels. The DCCT investigators noted that “the time, effort, and cost required were considerable” and “the resources needed are not widely available.” They concluded that “new strategies are needed to adapt methods of intensive treatment for use in the general community at less cost and effort.”

Although an exact duplication of the DCCT team may be unrealistic given the current healthcare system, a team approach remains optimal for preserving patients’ vision and quality of life. Primary care physicians need to maintain a high index of suspicion about diabetic retinopathy because it can be asymptomatic, and should regularly refer patients with diabetes to be screened by ophthalmologists. Ophthalmologists and primary care physicians should communicate regularly to develop regimens for patients and underscore for them the importance of glycemic and blood pressure control.

The American Diabetes Association (ADA) recently published a position statement about diabetic retinopathy. The position statement contains 4 principal recommendations about scheduling dilated retinal screening examinations:

- Patients with type 1 diabetes should have their first examination within 3 to 5 years after diagnosis of diabetes, but not before age 10 years. Follow-up examinations should be scheduled at least yearly thereafter.
- Patients with type 2 diabetes should have their first examination at the time of diagnosis of diabetes and yearly thereafter.
- Women with diabetes who plan to become pregnant should be counseled before conception about the risk of the development or progression of retinopathy. Once pregnant, women should have an eye examination during the first trimester, with the timing of follow-up examinations left to the discretion of the ophthalmologist. (Gestational diabetes does not increase the risk of diabetic retinopathy.)
- Both ophthalmologists and optometrists are qualified to conduct screening examinations, as long as they have experience in diagnosing diabetic retinopathy. However, patients with any sign of macular edema or retinopathy should be referred to an ophthalmologist.

The position statement notes that, based on evidence, the duration of diabetes before puberty may affect the development of microvascular complications. Therefore, the ADA suggests physicians may need to use their own judgment when choosing the timing of the first eye examination for
patients with type 1 diabetes. The statement also emphasizes that patients with abnormal findings should be re-examined more frequently.

CONCLUSION

Diabetic retinopathy can cause severe vision loss. More importantly, it may be a sign of systemic microvascular complications. These ocular and systemic complications of diabetes can be devastating for the patients in terms of morbidity and mortality. Thus, a team approach involving ophthalmologists, primary care physicians, and other healthcare professionals is remarkably important in preserving good general health and vision in patients with diabetes.

REFERENCES