CHAPTER 5

Diabetic Retinopathy

This chapter includes a related activity. Go to www.aao.org/bcscactivity_section12 or scan the QR code in the text to access this content.

Highlights

- Systemic control of hyperglycemia, hypertension, and hyperlipidemia is the foundation of care for all diabetic eye diseases.
- For treating proliferative diabetic retinopathy, both panretinal photocoagulation and intravitreal anti-VEGF therapy are effective. Panretinal photocoagulation may also be considered for eyes with severe nonproliferative diabetic retinopathy, especially in patients with type 2 diabetes. Anti–vascular endothelial growth factor (anti-VEGF) agents frequently reduce the severity of diabetic retinopathy and the risk of vision-threatening complications in eyes with nonproliferative disease but may not improve long-term visual outcomes.
- Intravitreal anti-VEGF is first-line therapy for most eyes with center-involved diabetic macular edema and vision loss. In contrast, treatment can generally be deferred in eyes with good vision despite center-involved diabetic macular edema.
- When anti-VEGF treatment is inappropriate or ineffective for diabetic macular edema, intravitreal corticosteroid therapy and macular focal/grid laser photocoagulation may be used as alternative or adjunctive therapy.

Introduction

Diabetic retinopathy is a leading cause of vision loss worldwide among patients aged 25–74 years, especially in resource-rich countries such as the United States. This chapter provides a foundation for the evaluation and treatment of diabetic retinopathy. See BCSC Section 1, *Update on General Medicine,* for discussion of diabetes mellitus. The following glossary provides the abbreviated and full names of diabetic retinopathy and diabetic and macular edema studies referenced in this chapter. Only the short names are used in the text.

Diabetic Retinopathy and Diabetic Macular Edema Studies

ACCORD Action to Control Cardiovascular Risk in Diabetes

ACCORDION ACCORD Follow-On Study

CLARITY Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy

DCCT Diabetes Control and Complications Trial

DRS Diabetic Retinopathy Study

DRVS Diabetic Retinopathy Vitrectomy Study

ETDRS Early Treatment Diabetic Retinopathy Study

FIELD Fenofibrate Intervention and Event Lowering in Diabetes

PANORAMA Study of the Efficacy and Safety of Intravitreal Aflibercept for the Improvement of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy

RIDE and RISE Ranibizumab Injection in Subjects with CSME With Center Involvement Secondary to Diabetes Mellitus

UKPDS United Kingdom Prospective Diabetes Study

VISTA Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema

VIVID Intravitreal Aflibercept Injection in Vision Impairment Due to Diabetic Macular Edema

WESDR Wisconsin Epidemiologic Study of Diabetic Retinopathy

Terminology and Classification

Diabetes Terminology

The American Diabetes Association classifies diabetes mellitus as type 1 diabetes (formerly, *insulin-dependent diabetes mellitus*) or type 2 diabetes (formerly, *non–insulin-dependent diabetes mellitus*). Type 1 diabetes results from the idiopathic or immune-mediated destruction of pancreatic β cells, which usually leads to absolute insulin deficiency. Type 2 diabetes is characterized by insulin resistance with or without insulin deficiency. Other classifications of diabetes mellitus recognized by the American Diabetes Association include a genetically mediated form secondary to endocrinopathy and drug- or chemical-induced diabetes.

Diabetic Retinopathy Terminology

Diabetic retinopathy is classified according to the severity and extent of hallmark diabetic lesions found within an eye. In *nonproliferative diabetic retinopathy (NPDR),* intraretinal

vascular changes are present, but extraretinal fibrovascular tissue does not develop. NPDR is staged across a spectrum of severity levels as mild, moderate, or severe. (Of note, although NPDR has been referred to as *background diabetic retinopathy,* this term is no longer used.) *Proliferative diabetic retinopathy (PDR)* is defined as the presence of retinal neovascularization due to diabetes-induced ischemia. It represents the most advanced level of diabetic retinopathy and may develop after an eye has progressed through the sequential stages of NPDR. Clinically, PDR is staged as either early disease or PDR with high-risk characteristics.

Diabetic macular edema (DME), or swelling of the central retina, results from abnormal vascular permeability and may develop in patients with diabetic retinopathy of any severity. DME is classified as *center-involved* (or *central-involved*) when the central 1-mm–diameter retinal subfield is thickened on optical coherence tomography (OCT); it is classified as *non–center-involved DME* when retinal thickening occurs only outside the central retinal subfield. *Clinically significant diabetic macular edema (CSME)* is an older term from the ETDRS that describes DME that meets certain severity criteria for size and location. However, this classification is no longer routinely used to determine the need for treatment.

In this chapter, research results are reported using terminology from the respective study being discussed, even though it may not conform to current usage.

Epidemiology of Diabetic Retinopathy

Diabetes mellitus is a growing global epidemic, projected to affect 700 million people by 2045, with a corresponding increase in the prevalence of diabetic retinopathy worldwide. Approximately one-third of the global population with diabetes mellitus also has diabetic retinopathy; of this group, one-third has a vision-threatening form of retinopathy.

Important long-term data on disease rates and progression, including a direct association between longer duration of both type 1 and type 2 diabetes and increased prevalence of diabetic retinopathy, were provided by the WESDR. Among WESDR participants with a 20-year history of diabetes mellitus, nearly 99% of those with type 1 disease and 60% of those with type 2 disease had some degree of diabetic retinopathy. PDR was also reported in 50% of patients with a 20-year history of type 1 diabetes and in 25% of those with a 25-year history of type 2 diabetes. In addition, a visual acuity of 20/200 or worse was observed in 3.6% of patients with younger-onset disease (ie, aged <30 years at diagnosis) and 1.6% of patients with older-onset disease (ie, aged 30 years or older at diagnosis). This vision loss was attributed to diabetic retinopathy in 86% of the younger-onset group and 33% of the older-onset group.

Of note, epidemiologic data from the WESDR study, first published in the 1980s, were drawn largely from White patients of northern European descent and therefore are not entirely applicable to other racial groups. Also, social determinants of health are increasingly recognized for their contributions to the increasing incidence of diabetes in the United States and the disproportionate effect of this disease on racial and ethnic minority groups and low-income adult populations. In 2011, data from the US Centers for Disease Control and Prevention indicated that the age-adjusted percentages of adults with a diagnosis of diabetes mellitus who reported visual impairment were 20.7%, 17.1%, and 15.6% among Black, White, and Hispanic participants, respectively. More recent studies indicate

that rates of diabetic retinopathy progression and vision loss have fallen with improvements in both systemic control of diabetes and treatments.

About diabetes: diabetes facts and figures. International Diabetes Federation Web site. Updated December 2, 2020. Accessed January 18, 2022. https://idf.org/about-diabetes/diabetes-facts-figures

Centers for Disease Control and Prevention. *National Diabetes Statistics Report 2020*. US Dept of Health and Human Services, Centers for Disease Control and Prevention; 2020. Accessed January 18, 2022. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

Klein R, Lee KE, Knudtson MD, Gangnon RE, Klein BE. Changes in visual impairment prevalence by period of diagnosis of diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology*. 2009;116(10):1937–1942.

Yau JW, Rogers SL, Kawasaki R, et al; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*. 2012;35(3):556–564.

Pathogenesis of Diabetic Retinopathy

Although the primary cause of diabetic microvascular disease remains poorly understood, exposure to hyperglycemia over time is known to adversely alter biochemical and molecular pathways. Changes include increases in inflammatory oxidative stress, advanced glycation end products, and plasma kallikrein and protein kinase C pathways, which ultimately cause endothelial damage and pericyte loss. Concomitant systemic factors, such as hypertension and hyperlipidemia, may exacerbate diabetic pathology. In addition, numerous hematologic abnormalities are associated with the onset and progression of retinopathy, including increased platelet adhesion, increased erythrocyte aggregation, and defective fibrinolysis. Diabetic neural pathology includes inner retinal layer thinning before development of clinically visible vascular lesions and perturbations in neural retinal function, as well as disorganization of neural retinal tissue in late-stage disease. However, the precise role of these abnormalities in the pathogenesis of retinopathy—individually or in combination—is not well defined.

Over time, changes in retinal capillaries, such as basement membrane thickening and selective loss of pericytes, lead to capillary occlusion and retinal nonperfusion. High-resolution imaging of the retinal vasculature, available through OCT angiography (OCTA) and adaptive optics scanning laser ophthalmoscopy, often reveals areas of vascular remodeling even in eyes with clinically mild diabetic retinopathy. These vascular abnormalities occur in both the superficial and deeper retinal capillary plexuses and worsen with increasing severity of diabetic retinopathy (Fig 5-1). In addition, endothelial barrier decompensation leads to serum leakage and retinal edema. In late stages of the disease, retinal neovascularization occurs in response to increased levels of intraocular VEGF, which is produced by ischemic retinal tissue.

Duh EJ, Sun JK, Stitt AW. Diabetic retinopathy: current understanding, mechanisms, and treatment strategies. *JCI Insight*. 2017;2(14):e93751.

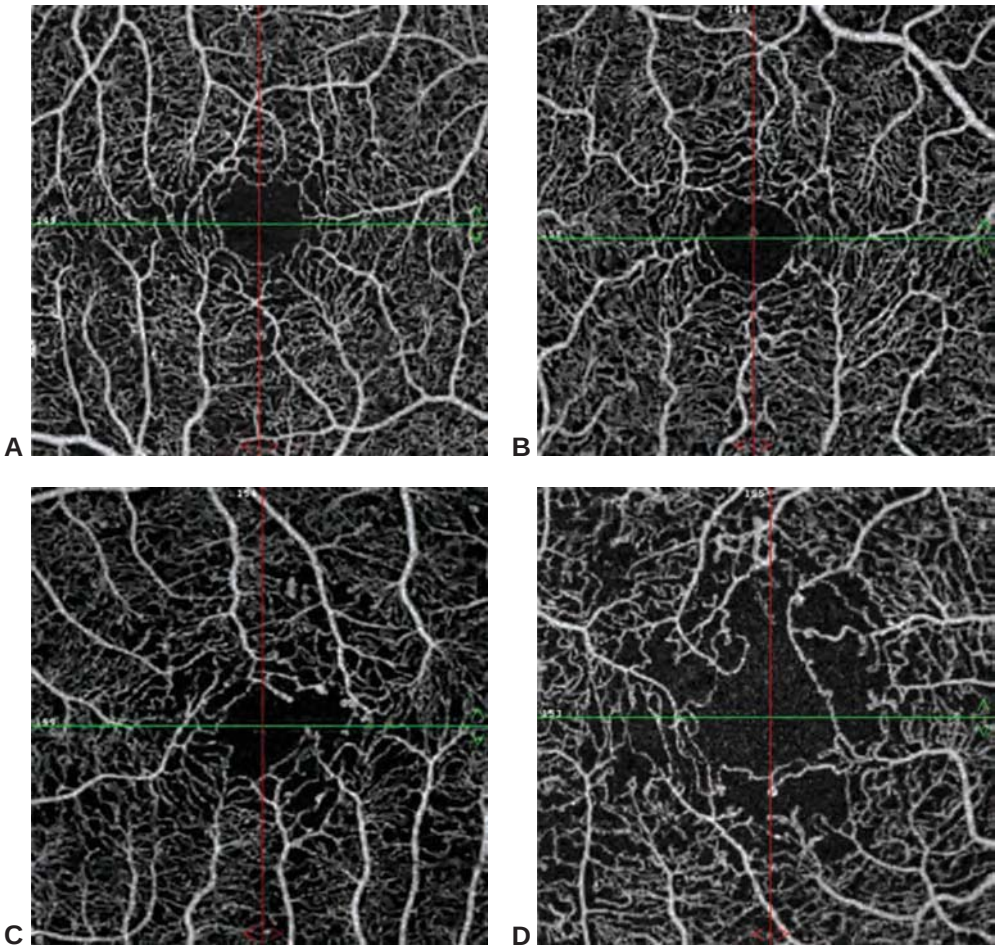

Figure 5-1 Optical coherence tomography angiography images demonstrate macular capillary nonperfusion and vascular tortuosity in diabetic eyes. The foveal avascular zone diameters in these images increase with worsening diabetic retinopathy severity level. **A,** Nondiabetic eye. **B,** Mild nonproliferative diabetic retinopathy (NPDR). **C,** Moderate NPDR. **D,** Proliferative diabetic retinopathy. *(Courtesy of Jennifer K. Sun, MD, MPH.)*

Recommended Diabetes Mellitus–Related Ophthalmic Examinations

In the first 5 years after a diagnosis of type 1 diabetes, advanced retinopathy is rare. In contrast, at initial diagnosis of type 2 diabetes, which may postdate the advent of hyperglycemia by years, a larger percentage of patients already have retinopathy and require concomitant ophthalmic examination.

Because pregnancy is associated with progression of diabetic retinopathy, pregnant women with diabetes mellitus may require more frequent retinal evaluations than the general population. An eye examination is recommended soon after conception and early

Table 5-1 Recommended Eye Examination Schedule for Patients With Diabetes Mellitus

Diabetes Type	Recommended Time of First Eye Examination	Routine Minimum Follow-up Interval
Type 1	5 years after diagnosis	Annually
Type 2	Upon diagnosis	Annually
Pregnant patients (type 1 or 2)	Soon after conception and early in the first trimester	For patients with no retinopathy to mild or moderate NPDR: every 3–12 months For patients with severe NPDR or worse: every 1–3 months

NPDR = nonproliferative diabetic retinopathy.

Modified from American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. *Diabetic Retinopathy.* American Academy of Ophthalmology; 2019. aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp

in the first trimester and at the discretion of the ophthalmologist thereafter (Table 5-1). Vision loss in pregnant women may occur from DME or from the complications of PDR. Although retinopathy may regress after delivery, high-risk PDR that develops just before or during pregnancy generally requires photocoagulation treatment. The frequency of follow-up visits during pregnancy depends on the severity of the retinopathy, history of blood glucose levels, and blood pressure control, as well as the need to identify worsening disease while it can still be treated in a timely fashion to prevent vision loss.

To help detect diabetic retinopathy and triage patients with the disorder, effective and efficient telemedicine screening approaches are needed globally to supplement in-person clinical examinations (Table 5-2). In recent years, artificial intelligence algorithms have successfully identified clinically referable cases of diabetic eye disease. Two of these systems, IDx-DR (Digital Diagnostics) and EyeArt (Eyenuk), are currently cleared by the US Food and Drug Administration for diabetic retinopathy screening, and the role of artificial intelligence in ocular telehealth systems is expected to grow. See BCSC Section 2, *Fundamentals and Principles of Ophthalmology,* for further discussion of artificial intelligence.

Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit Med*. 2018;1:39.

American Academy of Ophthalmology Retina/Vitreous Preferred Practice Pattern Panel. *Diabetic Retinopathy Preferred Practice Pattern*. American Academy of Ophthalmology; 2019. https://www.aao.org/education/preferred-practice-pattern/diabetic-retinopathy-ppp

Horton MB, Brady CJ, Cavallerano J, et al. Practice guidelines for ocular telehealth-diabetic retinopathy, third edition. *Telemed J E Health*. 2020;26(4):495–543.

Systemic Medical Management of Diabetic Retinopathy

Optimal glycemic control is by far the most important factor in the systemic management of diabetic retinopathy, as demonstrated by both the DCCT and the UKPDS (Table 5-3). In these studies, intensive glycemic control was associated with a reduced risk of new-onset

Table 5-2 Recommended Eye Examination Schedule Based on Diabetic Retinopathy Severity

Diabetic Retinopathy Severity	Presence of Macular Edema	Suggested Follow-up Interval (months)
Normal or minimal NPDR	No	12
Mild NPDR	No	12
	Non-CI DME	3–6
	CI DME[a]	1
Moderate NPDR	No	6–12
	Non-CI DME	3–6
	CI DME[a]	1
Severe NPDR[b]	No	3–4
	Non-CI DME	2–4
	CI DME[a]	1
Non–high-risk PDR[c]	No	3–4
	Non-CI DME	2–4
	CI DME[a]	1
High-risk PDR[c]	No	2–4
	Non-CI DME	2–4
	CI DME[a]	1
Inactive/involuted PDR	No	6–12
	Non-CI DME	3–4
	CI DME[a]	1

CI DME = center-involved diabetic macular edema; non-CI DME = non–center-involved diabetic macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.
[a] Consider intravitreal anti–vascular endothelial growth factor injection.
[b] Consider panretinal scatter laser surgery, especially in patients with type 2 diabetes.
[c] Consider panretinal scatter laser surgery or intravitreal anti–vascular endothelial growth factor injection.

Modified from American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. *Diabetic Retinopathy.* American Academy of Ophthalmology; 2019. aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp

retinopathy and with reduced progression of existing retinopathy in people with diabetes mellitus (type 1 in the DCCT and type 2 in the UKPDS). In addition, the DCCT showed that intensive glycemic control reduced progression to severe NPDR and PDR, the incidence of DME, and the need for panretinal and focal photocoagulation compared with conventional treatment. Even small but sustained changes in hemoglobin A_{1c} (HbA_{1c}) levels had a substantial effect on progression of diabetic retinopathy. Indeed, the delay in retinopathy onset and the reduction in disease progression and need for ocular surgery with intensive glycemic control were sustained over at least 2 decades, a "metabolic memory" that persisted even after the DCCT study ended and HbA_{1c} levels between the original randomization groups converged.

On the basis of the DCCT and UKPDS results, most patients with diabetes are now advised to achieve an HbA_{1c} level of less than 7.0%. The ACCORD trial and its follow-up, ACCORDION, found that further reduction in HbA_{1c} levels to less than 6.0% slowed diabetic retinopathy progression in patients with type 2 diabetes; however, this intensive regimen is not generally recommended because it is also associated with a greater mortality rate.

Effective management of comorbidities such as hypertension and hyperlipidemia can also reduce the risk of diabetic retinopathy worsening. When poorly controlled over many years, hypertension is associated with an increased risk of progression of diabetic retinopathy

Table 5-3 Seminal Trials in Diabetic Retinopathy Management

Study	Major Study Question(s)	Study Cohort	Randomization	Primary Results
Diabetes Control and Complications Trial (DCCT)	*Primary prevention study:* Will intensive control of blood glucose level slow development and subsequent progression of diabetic retinopathy (neuropathy and nephropathy)? *Secondary intervention study:* Will intensive control of blood glucose level slow progression of diabetic retinopathy (neuropathy and nephropathy)?	*Primary prevention study:* 726 patients with type 1 diabetes (1–5 years' duration) and no diabetic retinopathy. *Secondary intervention study:* 715 patients with type 1 diabetes (1–15 years' duration) and mild to moderate diabetic retinopathy.	Intensive control of blood glucose level (multiple daily insulin injections or insulin pump) vs conventional management.	In the primary prevention cohort, intensive control reduced the risk of developing retinopathy by 76%, and in the secondary intervention cohort, it slowed progression of retinopathy by 54%. In the 2 cohorts combined, intensive control reduced the risk of clinical neuropathy by 60% and albuminuria (nephropathy) by 54%.
United Kingdom Prospective Diabetes Study (UKPDS)	1. Will intensive control of blood glucose level in patients with type 2 diabetes reduce the risk of microvascular complications of diabetes, including the risk of retinopathy progression? 2. Will intensive control of blood pressure in patients with type 2 diabetes and elevated blood pressure reduce the risk of microvascular complications of diabetes, including the risk of retinopathy progression?	1. 4209 patients with newly diagnosed type 2 diabetes. 2. 1148 patients with hypertension and newly diagnosed type 2 diabetes.	1. Conventional policy starting with diet (1138 patients) vs an intensive policy starting with sulfonylurea—chlorpropamide (788 patients), glibenclamide (615 patients), or glipizide (170 patients) treatment—or treatment with insulin (1156 patients). If overweight and in the intensive group, patients were assigned to start treatment with metformin (342 patients). 2. Tight control of blood pressure (400 with ACE inhibitor and 398 with beta-blockers) vs less tight control (390 patients).	1. Intensive control of blood glucose level slowed progression of retinopathy and reduced the risk of other microvascular complications of diabetes mellitus. Sulfonylureas did not increase the risk of cardiovascular disease. 2. Intensive control of blood pressure slowed progression of retinopathy and reduced the risk of other microvascular and macrovascular complications of diabetes mellitus. No clinically or statistically significant difference was found in retinopathy outcomes when comparing blood pressure reduction with ACE inhibitors versus beta-blockers.

Study	Major Study Question(s)	Study Cohort	Randomization	Primary Results
Diabetic Retinopathy Study (DRS)	Is photocoagulation (argon or xenon arc) effective for treating diabetic retinopathy?	1742 participants with PDR or bilateral severe NPDR, with visual acuity of 20/100 or better in each eye.	1 eye randomly assigned to photocoagulation (argon or xenon arc) and 1 eye assigned to no photocoagulation.	At 5 years of follow-up, eyes treated with PRP had a reduction of 50% or more in rates of SVL compared with untreated control eyes. Thus, photocoagulation (argon or xenon arc) reduces the risk of SVL compared with no treatment. Treated eyes with high-risk PDR achieved the greatest benefit (see Fig 5-9). In the DRS, complications of argon laser PRP were generally mild but included a decrease in visual acuity by 1 or more lines in 11% of eyes and visual field loss in 5%.
Early Treatment Diabetic Retinopathy Study (ETDRS)	1. Is photocoagulation effective for treating DME? 2. Is photocoagulation effective for treating diabetic retinopathy? 3. Is aspirin effective in preventing progression of diabetic retinopathy?	3711 participants with mild NPDR through early PDR, with visual acuity of 20/200 or better in each eye.	1 eye randomly assigned to photocoagulation (scatter and/or focal) and 1 eye assigned to no photocoagulation; patients randomly assigned to 650 mg/day aspirin or placebo.	*Macular edema results:* Focal photocoagulation for DME decreased risk of moderate vision loss (doubling of initial visual angle), increased chance of moderate vision gain (halving of initial visual angle), and reduced retinal thickening. *Early scatter photocoagulation results:* Early scatter photocoagulation resulted in a small reduction in the risk of severe vision loss (<5/200 for at least 4 months), but is not indicated for eyes with mild to moderate diabetic retinopathy. Early scatter photocoagulation may be most effective in patients with type 2 diabetes. *Aspirin use results:* Aspirin use did not alter progression of diabetic retinopathy, increase risk of vitreous hemorrhage, or adversely affect vision. Aspirin use reduced risk of cardiovascular morbidity and mortality.

ACE = angiotensin-converting enzyme; DME = diabetic macular edema; DRCR = Diabetic Retinopathy Clinical Research; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; SVL = severe vision loss.

and DME. In contrast, the UKPDS showed that control of hypertension reduced progression of retinopathy and vision loss in patients with type 2 diabetes. Abnormally high lipid levels are associated with increased risk of vision loss from DME-associated hard exudates. Because hard exudates can resolve over time and with therapy, a fasting lipid panel should be checked in patients with extensive macular lipid deposits and treatment of hyperlipidemia initiated. Severe carotid artery occlusive disease may result in advanced PDR as part of ocular ischemic syndrome, whereas advanced diabetic nephropathy and anemia may exacerbate diabetic retinopathy.

Aiello LP, Sun W, Das A, et al; DCCT/EDIC Research Group. Intensive diabetes therapy and ocular surgery in type 1 diabetes. *N Engl J Med.* 2015;372(18):1722–1733.

Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy: The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. *Diabetes Care.* 1995;18(5):631–637.

Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. *Ophthalmology.* 1995;102(4):647–661.

UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837–853.

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ.* 1998;317(7160):703–713.

CLINICAL PEARL

In patients with diabetic retinopathy, vision loss is commonly associated with the following abnormalities:

- capillary leakage (DME)
- capillary occlusion (macular ischemia)
- sequelae from retinal ischemia (retinal neovascularization, vitreous hemorrhage, traction retinal detachment, neovascular glaucoma)

Nonproliferative Diabetic Retinopathy

In NPDR, retinal microvascular changes are limited to the retina and do not extend beyond the internal limiting membrane (ILM). Characteristic findings include intraretinal hemorrhages, microaneurysms, cotton-wool spots, intraretinal microvascular abnormalities (IRMAs), and dilation and beading of retinal veins. NPDR is generally graded as mild, moderate, or severe according to the extent and degree of clinical findings compared with standard photographs from the ETDRS (the photographs are discussed later in this section). More severe ETDRS retinopathy level at baseline has been associated with higher rates of progression to PDR.

To help clinicians identify patients at greatest risk of progression to PDR and high-risk PDR, the ETDRS investigators developed the 4:2:1 rule, which is based largely on

results from ETDRS Report Number 9 (see Table 5-3). According to this rule, severe NPDR manifests with any 1 of the following features:

- severe intraretinal hemorrhages (typically estimated as >20 intraretinal hemorrhages) and microaneurysms in 4 quadrants (Fig 5-2)
- definite venous beading in 2 or more quadrants (Fig 5-3)
- moderate IRMA in 1 or more quadrants (Fig 5-4)

In the ETDRS, patients with severe NPDR had 15% and 60% chances of progression to high-risk PDR within 1 and 3 years, respectively. In patients with *very severe NPDR,* which was defined as having 2 or more of the features in the preceding list, the chance of progression to high-risk PDR within 1 year increased to 45%.

The ETDRS severity scale has been the reference standard for classifying diabetic retinopathy for several decades. To use it, clinicians need to acquire and interpret standardized photographic fields that cover approximately 90° of the patient's posterior retina (eg, with ultra-wide-field imaging, >80% of the retina can now be visualized in a single 200° image). Peripheral diabetic retinopathy lesions are often present outside the standard ETDRS fields; in approximately 10% of eyes, these lesions suggest more severe diabetic retinopathy. Preliminary studies also suggest that a predominance of peripheral diabetic retinopathy lesions increases the risk of diabetic retinopathy progression. This association is being evaluated in the ongoing DRCR Retina Network (DRCR.net) Protocol AA study.

In more advanced cases of NPDR, retinal capillary nonperfusion is a common finding. Closure of retinal arterioles may expand areas of nonperfusion and progressive ischemia. In addition, the foveal avascular zone may appear increasingly irregular on fluorescein angiography (FA) or OCTA as well as enlarged when the innermost capillaries become nonperfused. With increasing retinopathy severity, macular vessel density decreases in the superficial and deep capillary plexuses. Peripheral nonperfusion is also frequently seen on ultra-wide-field FA (Fig 5-5), even in eyes with mild NPDR.

When NPDR leads to loss of visual function, 1 of 2 mechanisms is typically implicated: (1) increased intraretinal vascular permeability, resulting in macular edema (see

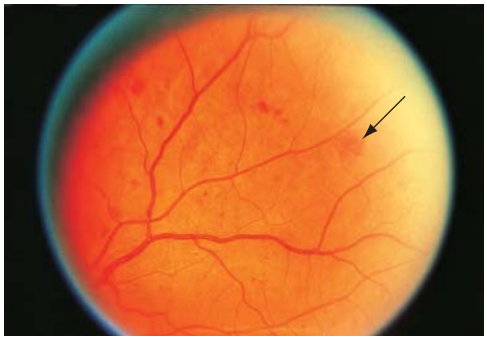

Figure 5-2 Fundus photograph shows diffuse intraretinal hemorrhages *(arrow)* and microaneurysms in an eye with NPDR. *(Standard photograph 2A, courtesy of the Early Treatment Diabetic Study [ETDRS].)*

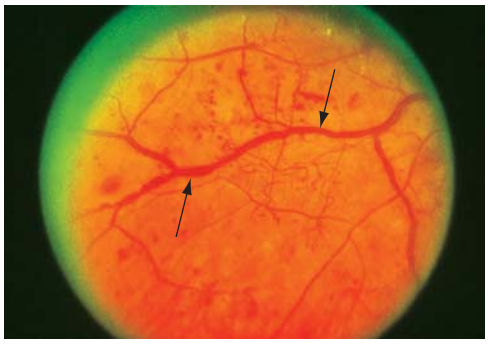

Figure 5-3 Fundus photograph shows venous beading *(arrows)* in an eye with NPDR. *(Standard photograph 6B, courtesy of the ETDRS.)*

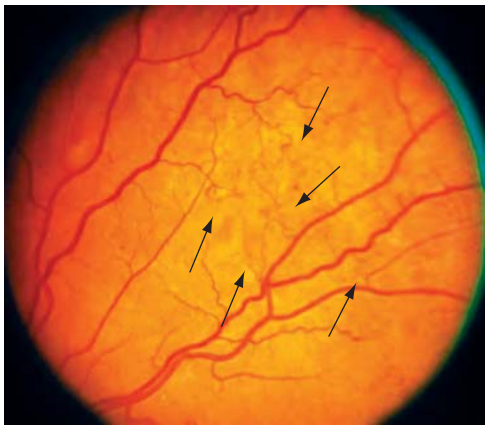

Figure 5-4 Fundus photograph demonstrates intraretinal microvascular abnormalities (IRMAs) *(arrows)* in an eye with NPDR. *(Courtesy of Jennifer K. Sun, MD, MPH.)*

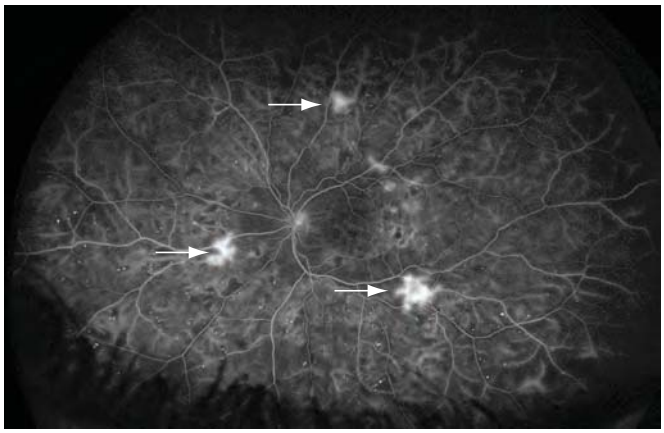

Figure 5-5 Ultra-wide-field fluorescein angiogram with focal areas of hyperfluorescence *(arrows)* representing leakage from retinal neovascularization along the vascular arcades. There are also patchy areas of hypofluorescence due to nonperfusion. *(Courtesy of Jennifer K. Sun, MD, MPH.)*

the section Diabetic Macular Edema later in this chapter); and (2) variable degrees of intraretinal capillary closure, resulting in macular ischemia.

Ashraf M, Sampani K, Clermont A, et al. Vascular density of deep, intermediate and superficial vascular plexuses are differentially affected by diabetic retinopathy severity. *Invest Ophthalmol Vis Sci*. 2020;61(10):53.

Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology.* 1991;98(5 Suppl):766–785.

Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991;98(5 Suppl): 786–806.

Silva PS, Cavallerano JD, Haddad NM, et al. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. *Ophthalmology*. 2015;122(5):949–956.

Treatment of Nonproliferative Diabetic Retinopathy

For eyes with NPDR without DME, there is no clear treatment mandate aside from systemic control of blood glucose, lipid, and hypertension levels. For patients with severe NPDR or worse, especially if they have type 2 diabetes or are unlikely to adhere to recommendations for follow-up or systemic control, early treatment with panretinal photocoagulation (PRP) should be considered. In eyes at all levels of NPDR, anti-VEGF therapy can reduce rates of vision-threatening complications and improve diabetic retinopathy severity. In addition, the DRCR Retina Network Protocol W study (Table 5-4) found that the cumulative probability of developing either center-involved DME with vision loss or PDR was reduced nearly threefold after 2 years of treatment with aflibercept versus sham injections. The PANORAMA trial, which also randomly assigned eyes to aflibercept versus sham treatment, showed that approximately 50% to 60% of eyes with moderately severe to severe NPDR at baseline improved by 2 or more levels on the ETDRS disease severity scale with aflibercept treatment. Despite improvements in anatomical outcomes in cohorts of eyes with good vision at baseline, neither Protocol W nor PANORAMA demonstrated gains in visual acuity with aflibercept treatment at 2 years. Both aflibercept and ranibizumab have been approved by the US Food and Drug Administration for use in diabetic retinopathy, including NPDR without DME; however, it is unclear at this time whether routine early treatment of eyes with NPDR is warranted given the lack of a clear long-term visual benefit.

Additional methods may improve diabetic retinopathy severity and slow the progression of diabetic retinal disease. For example, intravitreal steroid therapy for DME has been shown to reduce diabetic retinopathy severity. Similarly, in the ACCORD and FIELD studies, diabetic retinopathy progression was slowed in patients with type 2 diabetes after fenofibrate treatment, most likely independent of the drug's effects on blood lipid levels.

Bressler SB, Qin H, Melia M, et al; Diabetic Retinopathy Clinical Research Network. Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. *JAMA Ophthalmol*. 2013;131(8):1033–1040.

Chew EY, Ambrosius WT, Davis MD, et al; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med.* 2010; 363(3):233–244.

Ferris F. Early photocoagulation in patients with either type I or type II diabetes. *Trans Am Ophthalmol Soc*. 1996;94:505–537.

Maturi RK, Glassman AR, Josic K, et al; DRCR Retina Network. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W Randomized Clinical Trial. *JAMA Ophthalmol*. 2021;139(7):701–712.

Proliferative Diabetic Retinopathy

As retinopathy progresses, capillary damage and nonperfusion increase. Worsening retinal ischemia leads to release of vasoproliferative factors and the subsequent development of retinal neovascularization. VEGF, a major proangiogenic factor isolated from the vitreous of patients with PDR, may stimulate neovascularization of the retina, optic nerve head, or anterior segment.

Table 5-4 Selected DRCR Retina Network Studies

Protocol	Study Name	End Date	Study Conclusions
B	A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema	10/03/2008	At 2 years, focal/grid laser photocoagulation for center-involved DME was more effective and had fewer adverse effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone.
D	Evaluation of Vitrectomy for Diabetic Macular Edema Study	02/26/2009	Vitrectomy reduced retinal thickening in most eyes with DME and vitreomacular traction. Although VA outcomes improved by 10 or more letters in 38% of eyes, 22% lost 10 or more letters after vitrectomy.
I	Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination with Laser Photocoagulation for Diabetic Macular Edema	12/31/2013	At 2 years, intravitreal ranibizumab with prompt or deferred (≥24 weeks) focal/grid laser photocoagulation was more effective in increasing VA than focal/grid laser treatment alone or intravitreal triamcinolone with laser photocoagulation for the treatment of center-involved DME. In eyes with center-involved DME with vision impairment, focal/grid laser treatment at the initiation of intravitreal ranibizumab was no better, and was possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or longer.
P	A Pilot Study in Individuals with Center-Involved DME Undergoing Cataract Surgery	11/12/2010	This small observational study of eyes with DME undergoing cataract surgery revealed that only a small percentage of eyes experienced substantial VA loss or definitive worsening of DME after surgery.
Q	An Observational Study in Individuals with Diabetic Retinopathy without Center-Involved DME Undergoing Cataract Surgery	05/19/2011	A history of DME treatment and presence of non–center-involved DME are risk factors for development of center-involved DME after cataract surgery in eyes with diabetic retinopathy and no center-involved DME before surgery.
S	Prompt Panretinal Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy	02/05/2018	Ranibizumab injections are an effective alternative to PRP in treating PDR. At 2 and 5 years, VA outcomes with ranibizumab were noninferior to outcomes with PRP, whereas average VA over the 2-year (but not the 5-year) period was better with ranibizumab. Over 5 years, ranibizumab was associated with less peripheral field loss, reduced rates of DME onset, and fewer eyes requiring vitrectomy.
T	A Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab and Ranibizumab for Diabetic Macular Edema	10/18/2018	The 2-year clinical trial compared 3 drugs used to treat DME and found that gains in vision were greater for participants receiving aflibercept than for those receiving bevacizumab, but only among participants starting treatment with VA of 20/50 or worse. At 1 year, aflibercept showed superior gains compared with ranibizumab in this vision subgroup; however, a difference could not be identified at 2 years. The 3 drugs yielded similar gains in vision for patients with a VA of 20/32 or 20/40 at the start of treatment.

Protocol	Study Name	End Date	Study Conclusions
Tx	A Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab and Ranibizumab for Diabetic Macular Edema—Follow-up Extension Study	04/18/2019	Approximately two-thirds of eligible Protocol T participants completed a 5-year visit after study enrollment (2 years of study participation and 3 years of standard clinical care). Average vision at 5 years was better than the baseline value by 7.4 letters, but mean vision declined by nearly 5 letters between 2 and 5 years. Average OCT central subfield thickness remained stable from 2 to 5 years.
U	Short-term Evaluation of Combination Corticosteroid + Anti-VEGF Treatment for Persistent Central-Involved Diabetic Macular Edema Following Anti-VEGF Therapy	6/01/2017	In eyes with persistent DME and visual impairment despite previous anti-VEGF therapy, the dexamethasone + ranibizumab group experienced greater reduction of DME than the sham + ranibizumab group but no greater improvement in vision over 6 months.
V	Treatment for Central-Involved Diabetic Macular Edema in Eyes with Very Good Visual Acuity	09/11/2018	Eyes with good vision (20/25 or better) despite center-involved DME had similar rates of vision loss (ie, 5 or more letters lost) over 2 years whether they initially received intravitreal aflibercept, laser therapy, or observation (aflibercept was given to patients in the laser and observation groups who experienced vision loss during follow-up). At 2 years, all 3 groups had a mean VA of 20/20.
W	Intravitreous Anti-VEGF Treatment for Prevention of Vision-Threatening Diabetic Retinopathy in Eyes at High Risk	Anticipated 01/04/2022	Among eyes with moderate to severe NPDR, the proportion that developed PDR or center-involved DME with vision loss was lower with periodic aflibercept treatment than with sham treatment through at least 2 years. However, compared with aflibercept initiated after development of PDR or DME, preventive treatment with aflibercept did not confer visual benefits at 2 years.
AB	Intravitreous Anti-VEGF vs. Prompt Vitrectomy for Vitreous Hemorrhage from Proliferative Diabetic Retinopathy	01/09/2020	Eyes with vitreous hemorrhage from PDR that were randomly assigned to vitrectomy or intravitreal aflibercept had similar visual outcomes at 6 months and 2 years. On average, vitrectomy-treated eyes had faster early visual recovery. Approximately one-third of eyes in each group received the alternative treatment for PDR during the 2 years of the study.
AC	Randomized Trial of Intravitreous Aflibercept versus Intravitreous Bevacizumab + Deferred Aflibercept for Treatment of Central-Involved Diabetic Macular Edema	12/22/2021	Over 2 years, no significant difference in visual outcomes was found between eyes treated with aflibercept monotherapy vs those that started treatment with bevacizumab and were switched to aflibercept if visual improvement was suboptimal.

DME = diabetic macular edema; DRCR = Diabetic Retinopathy Clinical Research; NPDR = nonproliferative diabetic retinopathy; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; VA = visual acuity; VEGF = vascular endothelial growth factor.

Data from JAEB Center for Health Research. Diabetic Retinopathy Clinical Research Network (DRCR.net) website. Accessed October 11, 2022. www.drcr.net

Extraretinal fibrovascular proliferation, which defines PDR, progresses through 3 stages:

1. Fine new vessels with minimal fibrous tissue cross and extend beyond the ILM, often using the posterior hyaloid as a scaffold.
2. The new vessels grow in size and extent, developing an increased fibrous component.
3. The new vessels regress, leaving residual fibrovascular tissue that may be tethered within the posterior hyaloid.

In PDR, neovascular proliferation is categorized by its location: either on or within a disc diameter of the optic nerve head (neovascularization of the disc [NVD]) or elsewhere (neovascularization elsewhere [NVE]).

Patients may receive treatment at any stage of PDR. However, treatment is usually considered mandatory once an eye has developed high-risk characteristics, and it has been shown to dramatically reduce rates of severe vision loss. PDR with high-risk characteristics is defined as the presence of any of the following findings:

- any NVD with vitreous or preretinal hemorrhage
- extent of NVD greater than or equal to one-fourth the disc area, with or without vitreous or preretinal hemorrhage (ie, greater than or equal to the extent shown in ETDRS standard photograph 10A) (Fig 5-6)
- extent of NVE greater than or equal to one-half the disc area, with vitreous or preretinal hemorrhage (Fig 5-7)

In eyes that have not developed high-risk characteristics, treatment may be deferred. Treatment may also be deferred in eyes that have peripheral neovascularization outside the seven 30° photographic fields comprising the standard protocol for diabetic retinopathy

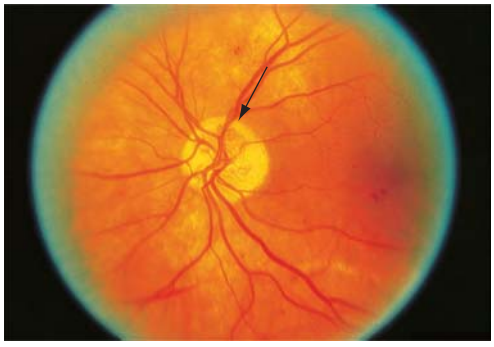

Figure 5-6 Fundus photograph of a left eye shows neovascularization of the disc (NVD, *arrow*) with a small amount of vitreous hemorrhage. Even without vitreous hemorrhage, this degree of neovascularization is the lower limit of moderate NVD and is considered high-risk proliferative diabetic retinopathy. *(Standard photograph 10A, courtesy of the Diabetic Retinopathy Study.)*

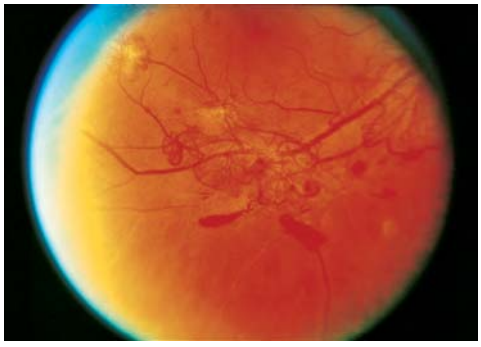

Figure 5-7 Fundus photograph of a right eye shows cotton-wool spots and moderate neovascularization elsewhere with preretinal hemorrhage. *(Standard photograph 7, courtesy of the Diabetic Retinopathy Study.)*

imaging set by the ETDRS, but that do not have accompanying intraocular hemorrhage. However, patients at especially high risk for diabetic retinopathy progression because of nonadherence or poor systemic control should be treated promptly.

Management of Proliferative Diabetic Retinopathy and Its Complications

The goals of PDR treatment are to control ischemia and reduce ocular VEGF levels so that neovascularization can involute or regress and the incidence of vitreous hemorrhage is reduced. This can be accomplished with either intravitreal administration of anti-VEGF drugs or ablation of ischemic retina via laser photocoagulation. Because of the contraction of fibrovascular tissue that can occur with either anti-VEGF therapy or PRP, treatment may be followed by increased vitreoretinal traction, recurring vitreous hemorrhage, traction (also called *tractional*) retinal detachment, and/or combined traction and rhegmatogenous retinal detachment. When appropriate, complications from PDR or its treatment (eg, vitreous hemorrhage and traction retinal detachment) may be addressed with vitreoretinal surgery.

Pharmacologic management of proliferative diabetic retinopathy

Anti-VEGF and steroid drugs Multiple studies of anti-VEGF drugs, including phase 3 trials for the treatment of DME, have shown that intravitreal administration (see the section Intravitreal Injections in Chapter 19 of this volume for a discussion of the injection procedure) of these agents is highly effective at regressing retinal neovascularization in eyes with PDR. This regression has been observed in both newly diagnosed cases and chronic, refractory disease. Potential complications from the use of anti-VEGF drugs to manage PDR include traction retinal detachments, retinal tears, and as mentioned previously, combined traction and rhegmatogenous retinal detachments related to the induced rapid contracture of fibrovascular tissue, sometimes referred to as the "crunch" phenomenon.

Because of its effectiveness in regressing intraocular neovascularization and its generally favorable safety profile, anti-VEGF therapy is a reasonable alternative or adjunctive therapy to PRP for many eyes with PDR. In the DRCR.net Protocol S study, eyes with active PDR were randomly assigned to treatment with either prompt PRP (ie, standard care) or intravitreal ranibizumab and deferred PRP (see Figure 5-8 for a simplified flowchart of the DRCR.net anti-VEGF treatment algorithm for PDR). At 2 and 5 years, visual outcomes were equivalent between treatment groups. However, ranibizumab did show some benefits over PRP, including better average vision over the first 2 years of treatment. In addition, over 5 years, the ranibizumab-treated group had less peripheral visual field loss, reduced rates of vitrectomy surgery, and fewer cases of DME onset with visual impairment. No substantial differences in rates of major cardiovascular adverse events were found between the treatment groups, and most eyes in the ranibizumab group were still receiving injections at 5 years. (For more information on DRCR.net studies, see the sidebar Selected DRCR Retina Network Studies.) Similarly, the CLARITY study reported superior visual outcomes after 1 year of aflibercept therapy versus PRP in patients with PDR.

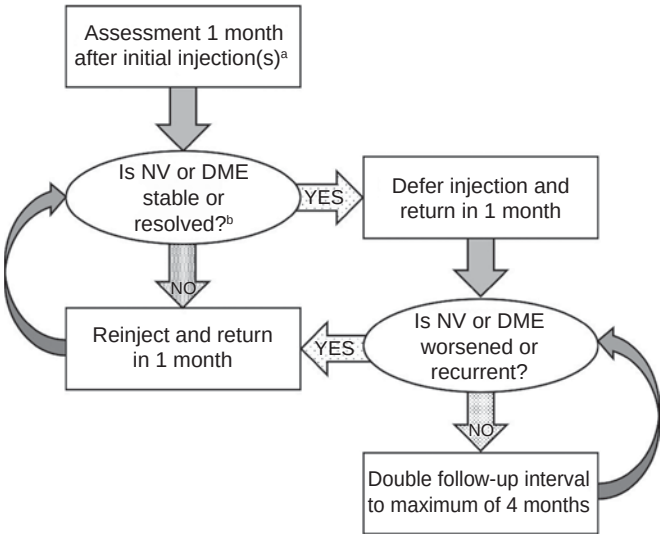

Figure 5-8 Simplified flowchart of the DRCR Retina Network anti-VEGF treatment algorithm for proliferative diabetic retinopathy and diabetic macular edema. DME = diabetic macular edema; NV = neovascularization; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; VEGF = vascular endothelial growth factor.
[a] In DRCR.net studies, an initial series of monthly injections was given for PDR or DME.
[b] PDR is considered stable once there is no improvement or worsening in NV over 2 injection visits. Resolved PDR is defined as the absence of any NV, including fibrous proliferation. DME is considered stable once there is no improvement or worsening in either visual acuity of 5 letters or more or OCT central subfield thickness of 10% or more over 2 injection visits. Resolved DME is defined as a normal central subfield thickness on OCT with visual acuity of 20/20 or better.
(Courtesy of Jennifer K. Sun, MD, MPH.)

SELECTED DRCR RETINA NETWORK STUDIES

The DRCR Retina Network (DRCR.net, formerly known as the *Diabetic Retinopathy Clinical Research Network*) conducts clinical research on diabetic eye disease, initiatives that typically involve community practices as well as academic centers. Since its inception in 2002, DRCR.net has conducted many of the studies underpinning current standard care practices for diabetic retinopathy and DME. See Table 5-4 earlier in this chapter and eTable 5-1, which provides an additional list of DRCR.net studies with primary results reported. Visit www.aao.org/bcscsupplement_section12 to view the eTable.

Anti-VEGF drugs can also cause beneficial involution of anterior segment neovascularization and can be successfully used to treat neovascular glaucoma, although long-term control is better achieved with PRP. In addition, when administered preoperatively, anti-VEGF drugs may be an adjunct to vitrectomy to manage complications of PDR. Of note, anti-VEGF injections should be given within a week of surgery to minimize the risk of vision-impairing traction retinal detachment.

Although anti-VEGF therapy is effective for PDR and offers some advantages over PRP, the decision to use these agents should be made on an individual basis. Once anti-VEGF therapy is selected, patients should adhere to near-monthly follow-up visits throughout the first 1–2 years of treatment. When the recommended follow-up intervals are ignored, recurrent and unchecked retinal neovascularization may occur, resulting in irreversible vision loss. For patients with medical instability or other limitations that may hinder adherence, treatment with PRP is more appropriate, as its effects may last for decades. In clinical practice, some physicians combine anti-VEGF and PRP treatments to take advantage of the respective advantages of each.

Although steroid agents are not used for primary treatment of PDR, they do reduce PDR-related outcomes in diabetic eyes. Combined rates of vitreous hemorrhage, need for PRP, and development of neovascularization (as viewed on fundus photographs or during a clinical examination) have decreased in eyes receiving intravitreal steroid therapy for non-PDR indications, such as DME.

Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med.* 1994;331(22):1480–1487.

Gross JG, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(10):1138–1148.

Sivaprasad S, Prevost AT, Vasconcelos JC, et al; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *Lancet*. 2017;389(10085):2193–2203.

Nonpharmacologic management of proliferative diabetic retinopathy

Laser treatment Over the last 4 decades (ie, until the recent advent of anti-VEGF therapy), the mainstay of treatment for PDR was thermal laser photocoagulation in a panretinal pattern to induce regression of neovascularization. Indications for photocoagulation are still largely based on findings from the DRS (Fig 5-9; see Table 5-3). For patients with high-risk PDR who are not already receiving anti-VEGF therapy, PRP treatment is almost always recommended. PRP destroys ischemic retina, thus reducing production of growth factors that promote disease progression, such as VEGF. PRP also increases oxygen tension in the eye via 2 mechanisms: (1) decreased oxygen consumption overall as a result of purposeful retinal destruction; and (2) increased diffusion of oxygen from the choroid in the areas of the photocoagulation scars. Collectively, these changes cause regression of existing neovascular tissue and prevent progressive neovascularization.

Laser treatment may be accomplished in a single session or over multiple sessions. The DRCR.net Protocol F study found no long-term vision benefits with multiple-session versus single-session laser administration. After the initial PRP, additional therapy may be applied incrementally in an attempt to achieve complete regression of persistent or recurrent neovascularization. As mentioned previously, some clinicians combine anti-VEGF therapy with PRP based on the premise that initial anti-VEGF therapy will regress neovascularization quickly and reduce onset or worsening of DME, whereas the effect of the PRP will endure for years, without the need for long-term intravitreal injections.

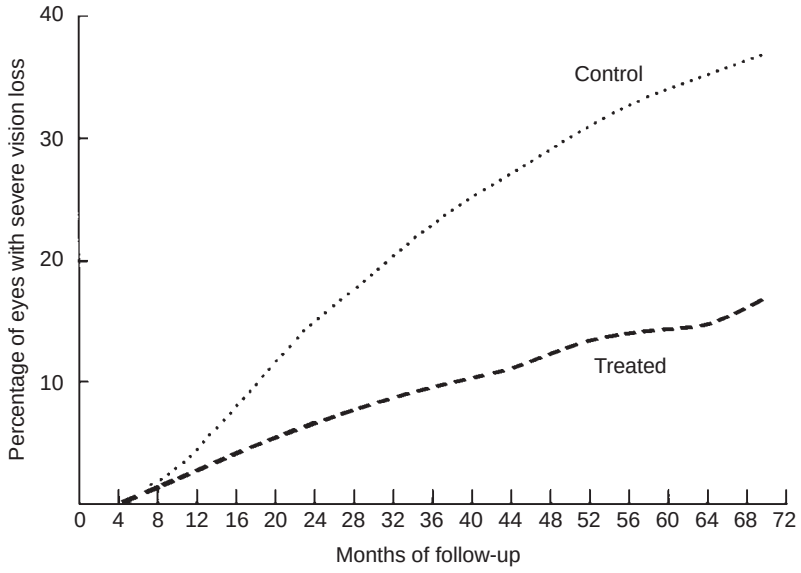

Figure 5-9 Comparison of argon laser and xenon arc treatment groups combined versus control groups in the Diabetic Retinopathy Study shows cumulative percentage of eyes that experienced severe vision loss during the follow-up period. *(Reprinted from Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of DRS findings, DRS report number 8.* Ophthalmology. *1981;88(7):583–600. ©1981, with permission from Elsevier.)*

Full PRP, as used in the DRS and ETDRS (see Table 5-3), included 1200 or more 500-μm burns created by using argon green or blue-green lasers, separated by one-half burn width (Fig 5-10). Although use of automated pattern scan lasers has increased in recent years, uncontrolled studies suggest that these treatments do not have equivalent effects in a burn-for-burn comparison.

Adverse effects of scatter PRP include choroidal detachment as well as decreases in peripheral field vision, night vision, color vision, contrast sensitivity, and in rare cases, pupillary dilation. After treatment, some patients may experience a transient loss of 1 or 2 lines of visual acuity or increased glare. Other transient adverse effects include loss of accommodation, loss of corneal sensitivity, and photopsias. Macular edema may also be precipitated or worsened by PRP. Sparing the horizontal meridians (ie, the path of the long ciliary vessels and nerves) protects accommodation, pupillary function, and corneal innervation. When necessary, heavy treatment should be performed in areas of the retina where vision loss is less noticed by patients (ie, the inferior retina) or in areas that are associated with a low likelihood of morbidity. Great care must be taken to avoid foveal photocoagulation, especially when image-inverting lenses are used.

Chew EY, Ferris FL III, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. *Ophthalmology.* 2003;110(9):1683–1689.

Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. *Ophthalmology.* 1981;88(7):583–600.

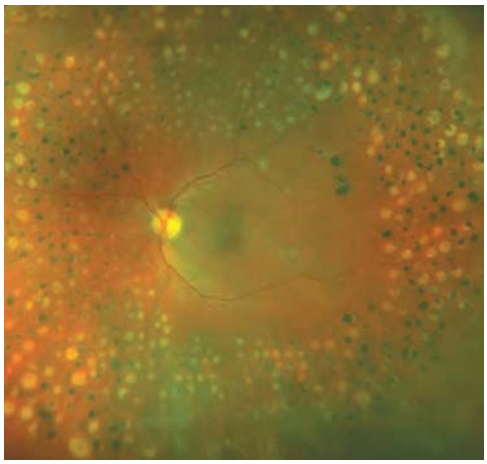

Figure 5-10 Fundus photograph shows an eye that has undergone panretinal photocoagulation treatment. Laser scars are characterized by either chorioretinal and retinal pigment epithelium (RPE) atrophy or RPE hyperpigmentation. *(Courtesy of Jennifer K. Sun, MD, MPH.)*

Vitrectomy In patients with PDR, indications for pars plana vitrectomy are

- nonclearing vitreous hemorrhage
- substantial recurring vitreous hemorrhage, despite use of maximal PRP
- dense premacular subhyaloid hemorrhage
- traction retinal detachment involving or threatening the macula
- combined traction and rhegmatogenous retinal detachment
- red blood cell–induced (erythroclastic) glaucoma and ghost cell glaucoma
- anterior segment neovascularization with media opacities preventing PRP

A more extensive discussion of the surgical management of PDR appears in the section Vitrectomy for Complications of Diabetic Retinopathy in Chapter 19 of this volume.

Recchia FM, Scott IU, Brown GC, Brown MM, Ho AC, Ip MS. Small-gauge pars plana vitrectomy: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2010;117(9):1851–1857.

Additional Vision-Threatening Complications of Diabetic Retinopathy

Neovascularization of the iris or anterior chamber angle

Small, isolated tufts of neovascularization at the pupillary border are relatively common in patients with diabetes mellitus. Treatment may be withheld in these eyes in favor of careful monitoring, with relatively short intervals between slit-lamp and gonioscopic examinations. However, treatment should be considered for eyes that have contiguous neovascularization of the pupil and iris collarette, with or without inclusion of the anterior chamber angle, and when wide-field FA reveals widespread nonperfusion or peripheral neovascularization. Treatment is usually PRP; intravitreal injection of anti-VEGF drugs may be used as a temporizing measure to reduce neovascularization until definitive PRP is administered. Development of peripheral anterior synechiae despite treatment with PRP or anti-VEGF may require glaucoma surgery.

Vitreous hemorrhage

The DRVS was a prospective randomized clinical trial published in 1985 that investigated the role of vitrectomy in the management of eyes with severe PDR. Benefits of early (1–6 months after onset of vitreous hemorrhage) versus late (1 year after onset) vitrectomy were evaluated. Eyes of patients with type 1 diabetes and severe vitreous hemorrhage clearly showed a benefit from earlier vitrectomy, whereas eyes of patients with type 2 or mixed diabetes did not.

In patients with PDR and no history of PRP, earlier intervention should be considered. In contrast, patients with previous, well-placed, complete PRP who have vitreous hemorrhage secondary to PDR may be observed for a longer period before intervention is initiated. In patients with dense, nonclearing vitreous hemorrhages, frequent ultrasonography studies are necessary to monitor for retinal detachment. When retinal detachment is discovered, the timing for the vitrectomy depends on the characteristics of the detachment. Patients with bilateral severe vitreous hemorrhage should undergo vitrectomy in 1 eye as soon as possible for vision rehabilitation. Recent advances in vitreoretinal surgery, including smaller-gauge instrumentation that shortens operating times and decreases complications, allow earlier intervention for nonclearing vitreous hemorrhage.

In the DRCR.net Protocol AB study, patients with vitreous hemorrhage from PDR were randomly assigned to vitrectomy versus intravitreal anti-VEGF therapy with aflibercept. Visual outcomes at 6 months and 2 years were similar between the groups. However, eyes treated with vitrectomy, especially those with worse baseline vision, recovered vision more quickly than eyes treated with anti-VEGF over the first 4–12 weeks.

Traction retinal detachment

Complications from PDR may be exacerbated by vitreous attachment to and traction on fibrovascular proliferative tissue, causing secondary traction retinal detachments. Partial posterior vitreous detachment frequently develops in eyes with fibrovascular proliferation, resulting in traction on the new vessels and vitreous or preretinal hemorrhage. Tractional complications such as vitreous hemorrhage, retinal schisis, retinal detachment, or macular heterotopia may ensue, as well as progressive fibrovascular proliferation. In addition, contraction of the fibrovascular proliferation and vitreous may result in retinal breaks and subsequent combined traction and rhegmatogenous retinal detachment.

Traction retinal detachment that does not involve the macula may remain stable for many years even when left untreated. However, when the macula becomes involved or is threatened, prompt vitrectomy is generally recommended.

Diabetic papillopathy

Unilateral or bilateral optic nerve head edema may occur in patients with diabetes, sometimes in association with DME from increased vascular leakage. Risk factors for diabetic papillopathy include a small cup–disc ratio or rapid reduction of glycemia; however, it can develop at any severity stage of diabetic retinopathy or level of glycemic control. Although there is no proven therapy for diabetic papillopathy, this condition generally has a good prognosis.

Diabetic Macular Edema

Diabetic macular edema results from a hyperglycemia-induced breakdown of the blood–retina barrier, which leads to fluid extravasation from retinal vessels into the surrounding neural retina (Fig 5-11). A diagnosis of DME is made when retinal thickening involves the macula. DME may be associated with hard exudates, which are precipitates of plasma lipoproteins that may persist after DME resolution.

In patients with diabetes, central subfield–involved DME that affects the fovea is a common cause of vision loss. In contrast, non–center-involved DME is unlikely to affect vision unless it progresses to center involvement. Although DME is increasingly common

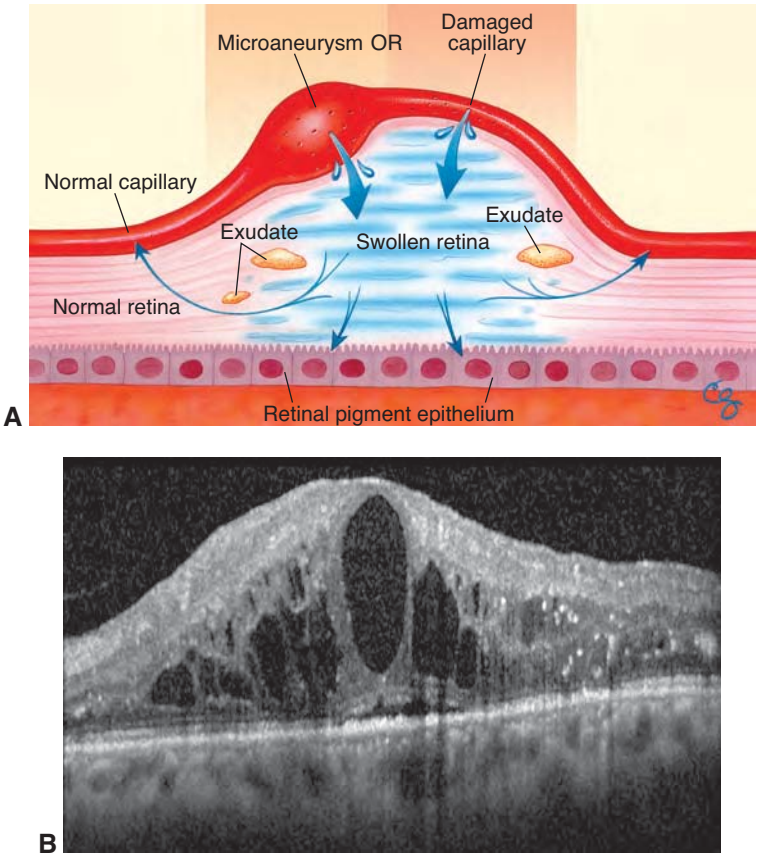

Figure 5-11 Diabetic macular edema (DME). **A,** Artist's rendering of the mechanism of DME, demonstrating development of retinal thickening from a breakdown of the blood–retina barrier. **B,** Spectral-domain OCT scan of DME. Although there are extensive cystic changes in the outer plexiform and outer nuclear layers, the external limiting membrane line appears intact across the extent of the scan, with the exception of shadowing artifacts from more superficial hyperreflective lesions. Note the foveal detachment. *(Part A from Ginsburg LH, Aiello LM. Diabetic retinopathy: classification, progression, and management.* Focal Points: Clinical Modules for Ophthalmologists. *American Academy of Ophthalmology; 1993, module 7. Illustration by Christine Gralapp. Part B courtesy of Colin A. McCannel, MD.)*

among eyes with more advanced diabetic retinopathy, DME may occur with diabetic retinopathy of any severity. Even patients with mild NPDR may experience substantial vision loss from highly thickened retinas.

Imaging studies are useful for diagnosing DME. FA depicts the breakdown of the blood–retina barrier by showing local areas of retinal capillary leakage. However, leakage may also be observed on an angiogram in the absence of macular retinal thickening. OCT and slit-lamp biomicroscopy are the most appropriate studies for detecting macular thickening (Fig 5-12; Activity 5-1).

ACTIVITY 5-1 OCT Activity: OCT of diabetic macular edema.
Courtesy of Colin A. McCannel, MD.

Classification of Diabetic Macular Edema

Diabetic macular edema is classified as center involved or non–center involved (Fig 5-13) by using algorithms based on a simple, OCT-related definition. Quantitative thresholds for abnormal thickening of the 1-mm-diameter OCT central subfield vary according to machine type and, on average, are thicker in men than in women (see Fig 5-12).

The prospective, randomized ETDRS was the first study to establish standard treatment paradigms for managing DME in patients with diabetes and non–high-risk PDR (see Table 5-3). It defined *clinically significant diabetic macular edema (CSME)* with the following features as an indication for focal laser photocoagulation treatment:

- retinal thickening located at or within 500 μm of the center of the macula
- hard exudates at or within 500 μm of the center if associated with thickening of adjacent retina
- a zone of thickening larger than 1 disc area that is located within 1 disc diameter of the center of the macula

As mentioned previously, CSME is an older term that predates use of OCT to diagnose DME. Now that anti-VEGF treatment has supplanted macular laser photocoagulation as first-line therapy for DME, the CSME diagnosis, which is made clinically, is less relevant.

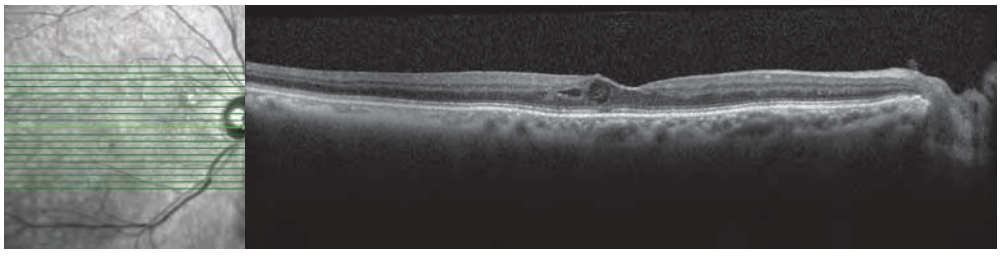

Figure 5-12 OCT volume scan of an eye with DME from a 75-year-old Hispanic man with a long history of poorly controlled type 2 diabetes (hemoglobin A_{1c} levels typically in the 9–9.6 range). The right eye has moderate NPDR. The patient previously underwent treatment with bevacizumab and aflibercept, but there is persistent center-involved DME. The cystic changes involving the temporal and inferior foveal regions are most noticeable in slices 10 through 7 in Activity 5-1. *(Courtesy of Colin A. McCannel, MD.)*

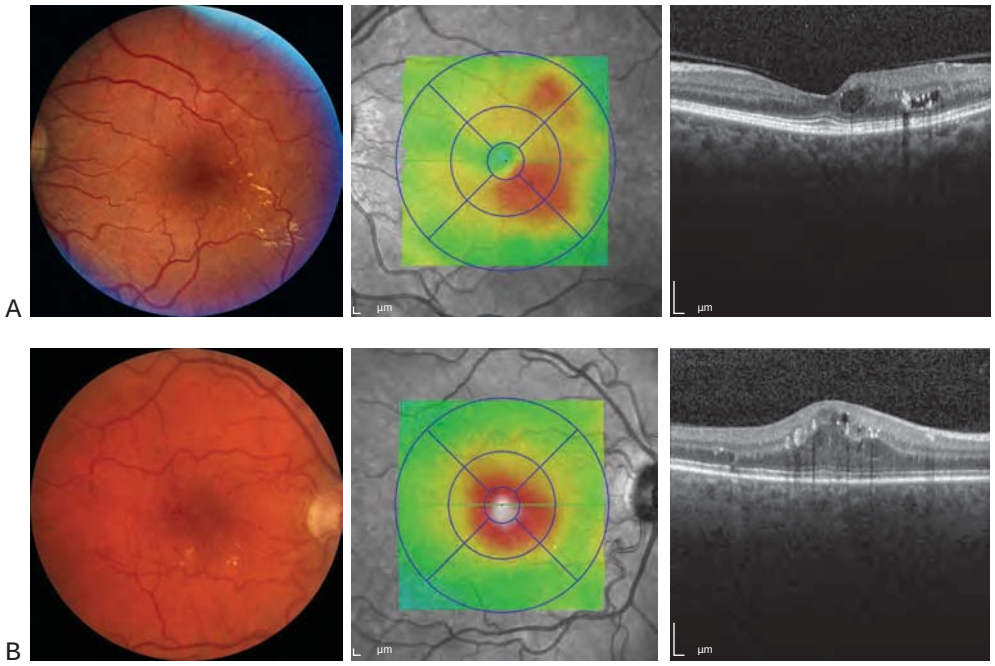

Figure 5-13 Imaging of eyes with DME on fundus photography and OCT. **A,** Eye with non–center-involved DME. **B,** Eye with center-involved DME. *(Courtesy of Jennifer K. Sun, MD, MPH.)*

Whether it is center involved or non–center involved, DME may manifest as focal or diffuse retinal thickening. Focal macular edema is characterized by areas of local fluorescein leakage from specific capillary lesions, such as microaneurysms. Diffuse macular edema is characterized by extensive retinal capillary leakage and widespread breakdown of the blood–retina barrier, often accumulating in a cystoid configuration in the perifoveal macula (ie, cystoid macular edema). Studies have shown no differences in treatment response based on pattern of macular edema, whether focal, diffuse, or a combination of these.

Management of Diabetic Macular Edema

To maximize visual function and prevent progressive vision loss in eyes with DME, ocular therapies should be considered in parallel with medical management and optimization of patient health habits. When macular edema is center involved and affects visual acuity, treatment is typically indicated. When patients are asymptomatic or have normal visual acuity, the decision to treat DME becomes more complex, as the condition may resolve spontaneously. In general, treatment may be safely deferred in eyes with good visual acuity despite center-involved DME as long as patients are followed up closely and therapy is instituted when vision worsens. Factors for consideration include the proximity of exudates or thickening to the fovea; the status and course of the fellow eye; any anticipated cataract surgery; the presence of high-risk PDR; treatment risks; any systemic conditions or medications (eg, thiazolidinediones) that may exacerbate or cause edema; and systemic control

of glycemia, hypertension, and hyperlipidemia. Ideally, DME treatment is initiated before scatter photocoagulation and cataract surgery are performed to reduce the risk of DME from these interventions.

Pharmacologic management of diabetic macular edema

Anti-VEGF drugs are first-line therapy for most eyes with center-involved DME, especially those with visual impairment caused by the DME. Corticosteroids are alternative agents for eyes that are not candidates for anti-VEGF therapy or in some eyes that were incompletely responsive to previous anti-VEGF treatment.

Anti-VEGF drugs Clinical trials have shown that anti-VEGF treatment is generally beneficial for eyes with DME. The DRCR.net Protocol I study was the first phase 3 trial to demonstrate that visual acuity outcomes with intravitreal anti-VEGF therapy were superior to outcomes with laser treatment for center-involved DME. This study revealed that intravitreal ranibizumab combined with prompt or deferred (≥24 weeks) focal/grid laser treatment was more effective in increasing visual acuity than focal/grid laser treatment alone or in combination with triamcinolone acetonide injections at both 1- and 2-year follow-up. After 1 year of treatment, eyes in the ranibizumab-treated groups gained an average of 8 or 9 letters of visual acuity versus those in the laser monotherapy group, which gained an average of only 3 letters. Through 5 years of follow-up, eyes in the ranibizumab treatment groups maintained the vision gains accrued in the first year of therapy, despite a progressively decreasing number of injections (Fig 5-14). Results from this study also suggest that for DME, adding focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and is possibly worse, for vision outcomes than deferring laser treatment for 24 weeks or more.

RISE and RIDE, 2 additional parallel phase 3 trials with identical study designs, indicated that compared with sham injections, ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME, with low rates of complications. Phase 3 trials have also demonstrated excellent efficacy of aflibercept for treatment of DME. In the VIVID and VISTA trials, an initial phase of 5 monthly injections of aflibercept followed by 148 weeks of either monthly or bimonthly therapy provided substantial visual acuity gains compared with laser photocoagulation therapy.

Although all available anti-VEGF agents are effective in treating DME, results from the DRCR.net Protocol T study demonstrated the superiority of aflibercept over bevacizumab in improving ETDRS visual acuity after both 1 and 2 years of treatment (see Figure 5-8 for a simplified flowchart of the DRCR.net anti-VEGF treatment algorithm for DME). Aflibercept was also superior to ranibizumab at 1-year follow-up but was statistically similar to ranibizumab at 2 years. The differences between the agents were due to the effects of these agents in eyes with worse (ie, ≤20/50) baseline vision. In eyes with milder visual impairment (ie, 20/32 to 20/40), results were equivalent for all 3 treatments at both 1 and 2 years. At 2 years, visual acuity improvements of 10 or more letters were observed in 50%, 41%, and 46% of the aflibercept, bevacizumab, and ranibizumab groups, respectively. In contrast, in eyes with worse visual impairment, 2-year improvement of 10 or more letters was observed in 76%, 66%, and 71% of aflibercept, bevacizumab, and

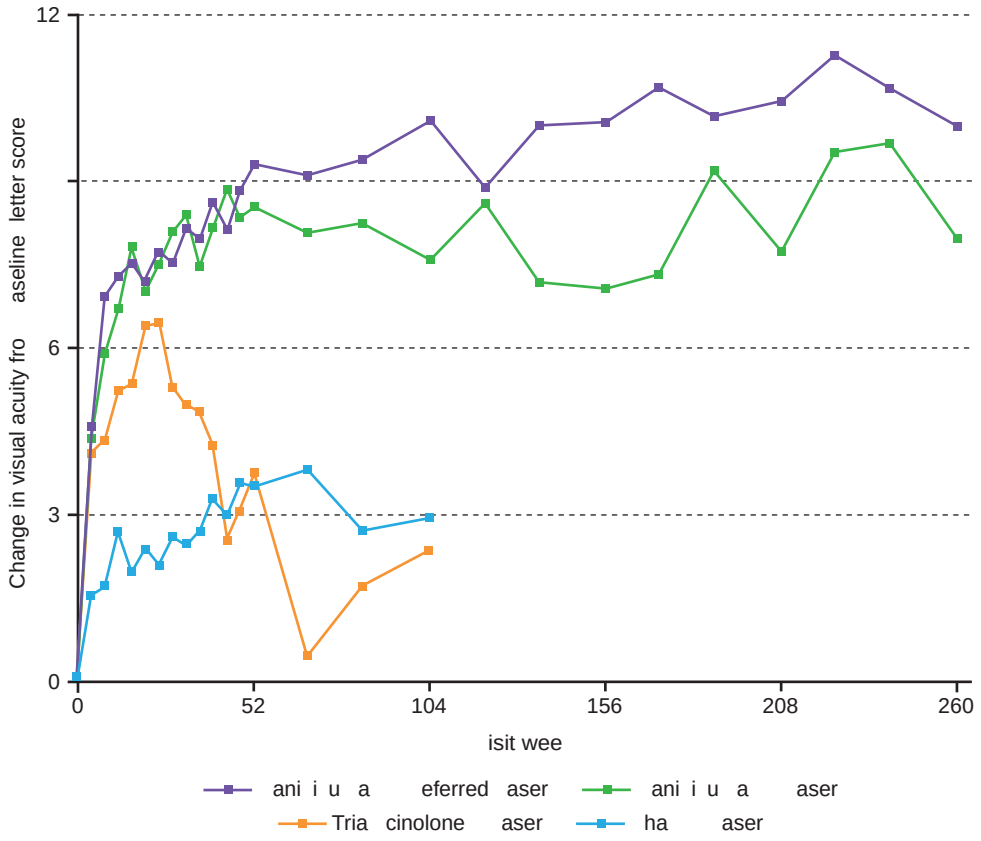

Figure 5-14 Results of the DRCR.net Protocol I study through 5 years demonstrating the superior visual acuity outcomes of treatment with ranibizumab with either prompt or deferred laser treatment compared with laser alone or in combination with triamcinolone through 2 years. Starting in the third year, only patients originally assigned to the ranibizumab groups were followed up. Results from years 3 to 5 suggest that treatment with ranibizumab plus prompt laser therapy is no better than ranibizumab with deferred laser treatment. *(Reprinted from Diabetic Retinopathy Clinical Research Network; Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results.* Ophthalmology. *2012;119(11):2312–2318. © 2012, with permission from Elsevier.)*

ranibizumab groups, respectively. Rates of substantial vision loss were low in all 3 treatment groups. A more recent study, DRCR.net Protocol AC, compared aflibercept monotherapy to initiation of treatment with bevacizumab first and switching to aflibercept if improvement was suboptimal. This trial demonstrated that over 2 years, visual outcomes were similar between these approaches in eyes with moderate visual impairment from DME.

In general, anti-VEGF agents are well tolerated. Serious intraocular events such as endophthalmitis are rare, with a prevalence of approximately 1 in 1000 injections. Although systemic thromboembolic events are known to be associated with systemic anti-VEGF administration, they have not been shown to be more common among patients who receive intraocular anti-VEGF treatment.

Although anti-VEGF therapy is indicated for most eyes with center-involved DME and visual impairment of 20/32 or worse, in eyes with DME and better vision, a strategy of initial observation with treatment only when vision worsens is generally safe. In the DRCR .net Protocol V study, eyes with visual acuity of 20/25 or better despite center-involved DME were randomly assigned to aflibercept therapy, macular laser treatment, or initial observation. Eyes in the laser and observation groups were given aflibercept if visual acuity worsened during study follow-up. At 2 years, rates of 1 line or greater vision loss (ie, decrease of 5 or more letters) were not significantly different between the groups, and all groups had mean visual acuity of 20/20. In the observation and laser groups, two-thirds and three-fourths of eyes, respectively, did not require aflibercept over the course of the study.

Corticosteroids Corticosteroids are generally used as second-line agents for DME because of studies that have demonstrated inferiority of visual outcomes with steroids versus other therapies and because of the high proportion of eyes that develop adverse effects with continued steroid use. At 2 years in the DRCR.net Protocol B trial, treatment of DME with focal/grid laser photocoagulation was more effective and caused fewer adverse effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone acetonide. Similarly, the DRCR.net Protocol I trial showed that at 2 years, treatment with intravitreal triamcinolone acetonide combined with laser therapy was inferior to treatment with ranibizumab with or without laser therapy as well as to laser treatment alone. A number of small studies initially suggested that intravitreal triamcinolone acetonide benefited patients with refractory DME. However, the DRCR.net Protocol U study, which evaluated eyes with persistent center-involved DME and visual impairment despite at least 6 prior injections of anti-VEGF agents, demonstrated that combination therapy with continued anti-VEGF treatment and a dexamethasone implant did not provide superior vision gains compared with continued anti-VEGF treatment alone. Eyes in the combination group did show greater improvements in retinal thickening over the 6-month study period, but this anatomical benefit was not associated with functional gains. Rates of cataracts and glaucoma are also higher in steroid-treated eyes than in anti-VEGF–treated eyes.

Nonetheless, corticosteroids are beneficial in some patients with DME. Studies of 2 types of sustained-release steroid implants, one made of dexamethasone and the other made of fluocinolone acetonide, reported improved visual acuity of 3 or more lines in eyes with DME. In patients with DME who have already undergone cataract surgery, steroid treatment may be a reasonable alternative to anti-VEGF therapy. In the DRCR.net Protocol I, visual acuity results in steroid-treated eyes that were pseudophakic at baseline (ie, they could not develop cataracts as a result of steroid treatment) were similar to those in anti-VEGF–treated eyes and were superior to results in the laser-treated group.

Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*. 2019;321(19):1880–1894.

Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904–1914.

Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626–635.e2.

Elman MJ, Ayala A, Bressler NM, et al; Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology.* 2015;122(2):375–381.

Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193–1203.

Nonpharmacologic management of diabetic macular edema

There are 2 nonpharmacologic interventions for DME: laser treatment and surgery. Macular focal/grid laser photocoagulation retains an important role as adjunctive treatment in eyes that are resistant to anti-VEGF agents; it is also an occasional first-line treatment in eyes with DME resulting from non–central focal leakage, which can be easily targeted by the laser. In addition, laser therapy may be a useful first-line treatment for patients who are not good candidates for anti-VEGF therapy because they are medically unstable or who are unable to adhere to near-monthly anti-VEGF treatment, especially in the first year. Pars plana vitrectomy, with or without ILM peeling, is often effective in improving retinal thickening in eyes with DME, especially when there is traction from the vitreous or an overlying epiretinal membrane; however, it does not always improve vision. Furthermore, definitive studies are needed to clearly define the role of vitrectomy in DME treatment.

Laser treatment Although anti-VEGF therapy has largely supplanted laser photocoagulation in the treatment of DME, laser therapy is well proven and causes minimal adverse events. Compared with observation alone in the ETDRS, macular focal/grid laser photocoagulation treatment of CSME reduced the risk of moderate vision loss, increased the chance of vision improvement, and was associated with only minor visual field loss. In contrast, eyes with DME that did not meet the criteria for CSME showed no benefit with laser treatment over the control group at 2 years.

Potential adverse effects of macular laser therapy include paracentral scotomata, transient increases of edema and/or decreases in vision, laser scar expansion, subretinal fibrosis, choroidal neovascularization, and inadvertent foveal burns. Clinical features associated with poorer visual acuity outcomes after photocoagulation treatment for DME include macular ischemia (extensive perifoveal capillary nonperfusion) and hard exudates in the fovea.

During treatment of DME, FA, along with an OCT thickness map, may be used to guide the laser. The laser parameters differ from those used in PRP and typically include spot sizes of 50–100 μm and burn durations of 0.1 second or less. For focal leakage, direct laser treatment using green or yellow wavelengths is applied to all leaking microaneurysms between 500 μm and 3000 μm from the center of the macula. For diffuse leakage or zones of capillary nonperfusion in the macula, a light-intensity grid pattern may be applied. Burns are typically separated by 1 burn width, and a green- or yellow-wavelength laser is used. Treatment should include areas of diffuse leakage more than 500 μm from the center of the macula and 500 μm from the temporal margin of the optic nerve head. Laser

sessions are repeated as often as every 16 weeks until retinal thickening has resolved or all leaking microaneurysms have been adequately treated.

Some studies suggest that micropulse therapy, or subthreshold intensity burns, is as effective as standard macular laser treatment while reducing damage to the retinal pigment epithelium and outer retinal layers. In eyes with DME, treatment of peripheral nonperfusion as visualized on ultra-wide-field FA with scatter photocoagulation does not improve vision or retinal thickening.

Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 2. *Ophthalmology.* 1987;94(7):761–774.

Vitrectomy When posterior hyaloidal traction or an associated epiretinal membrane leading to mechanical traction is present, creation of a posterior vitreous detachment and possible ILM or epiretinal membrane peeling can help reduce retinal thickening. The use of vitrectomy as first-line therapy for DME without vitreomacular traction is uncommon in the United States; however, it is more prevalent internationally.

Although vitrectomy generally improves retinal thickening in eyes with DME, multiple studies have reported inconsistent effects of the procedure on visual acuity in eyes with DME, despite consistent improvements in edema. In the DRCR.net Protocol D study, a prospective observational case series, retinal thickening was reduced in most eyes after vitrectomy; however, median visual acuity remained unchanged over the 6-month follow-up period.

Haller JA, Qin H, Apte RS, et al; Diabetic Retinopathy Clinical Research Network Writing Committee. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology.* 2010;117(6):1087–1093.e3.

Jackson TL, Nicod E, Angelis A, Grimaccia F, Pringle E, Kanavos P. Pars plana vitrectomy for diabetic macular edema: a systematic review, meta-analysis, and synthesis of safety literature. *Retina*. 2017;37(5):886–895.

Cataract Surgery in Patients With Diabetes Mellitus

Various studies suggest that the severity of both diabetic retinopathy and DME may worsen after cataract surgery. In the DRCR.net Protocol Q trial, patients with NPDR but no preoperative center-involved DME were more likely to develop postoperative DME after cataract surgery if they had non–center-involved DME or a history of DME treatment before surgery. In the Protocol P study, which enrolled patients with preexisting DME, a small percentage of eyes had substantial visual acuity loss or definitive progression in central retinal thickening after cataract surgery. Therefore, in clinical practice, a preoperative anti-VEGF or steroid injection is typically given to patients with center-involved DME who are about to undergo cataract surgery. In addition, control of systemic factors should be optimized as much as possible before surgery.

In patients with severe NPDR or PDR, scatter photocoagulation should be considered before cataract removal if the ocular media are sufficiently clear to allow for treatment. When the density of the cataract precludes adequate evaluation of the retina or treatment, prompt

postoperative retinal evaluation and treatment are recommended. In general, all patients with preexisting diabetic retinopathy should be reevaluated after cataract surgery.

Cataract surgeons should be mindful of the need for regular retinal evaluations postoperatively and possible surgical interventions in the future. They should perform an adequate capsulorrhexis to prevent anterior capsular phimosis and should avoid the use of silicone lenses in diabetic eyes, as these lenses may fog with condensation during subsequent vitrectomies. The use of multifocal lenses may also complicate future surgical approaches and may result in unsatisfactory visual outcomes in patients with macular disease. BCSC Section 11, *Lens and Cataract,* briefly discusses issues that should be considered by the cataract surgeon when treating patients with diabetes mellitus.

Baker CW, Almukhtar T, Bressler NM, et al; Diabetic Retinopathy Clinical Research Network Authors/Writing Committee. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. *JAMA Ophthalmol*. 2013;131(7):870–879.

Bressler SB, Baker CW, Almukhtar T, et al; Diabetic Retinopathy Clinical Research Network Authors/Writing Committee. Pilot study of individuals with diabetic macular edema undergoing cataract surgery. *JAMA Ophthalmol*. 2014;132(2):224–226.

CHAPTER 6

Retinal Vascular Diseases Associated With Cardiovascular Disease

This chapter includes related activities. Go to www.aao.org/bcscactivity_section12 or scan the QR codes in the text to access this content.

Highlights

- Retinal venous and arterial occlusions are frequently associated with systemic disease and represent a unique opportunity for the ophthalmologist to contribute to a patient's general medical care. The most common associations are hypertension, diabetes, and atherosclerosis; but inflammatory, infectious, or hematologic disorders can also be identified.
- Retinal artery occlusion is a medical emergency that must be regarded as a "stroke equivalent," requiring immediate evaluation for carotid and cardiac disease.
- Pharmacologic therapy is presently the standard of care for macular edema associated with retinal vein occlusion. Intravitreal injection of anti–vascular endothelial growth factor (anti-VEGF) agents is the first-line treatment, and intravitreal corticosteroid may be helpful as a second-line or adjunctive treatment in recalcitrant cases.
- Cases of artery occlusion without obvious emboli must be evaluated for giant cell arteritis, which can result in bilateral blindness if not treated promptly and correctly.

Systemic Arterial Hypertension and Associated Ocular Diseases

Elevated blood pressure (BP) is defined as systolic BP of 120–129 mm Hg *and* diastolic BP less than 80 mm Hg. Stage 1 hypertension is defined as 130–139 mm Hg systolic *or* 80–89 mm Hg diastolic. Ocular effects of hypertension can be observed in the retina, choroid, and optic nerve. Retinal changes can be described and classified with the use of ophthalmoscopy and angiography. An ophthalmologist's recognition of posterior segment vascular changes may prompt the initial diagnosis of hypertension. BCSC Section 1, *Update on General Medicine,* discusses hypertension in more detail.