Diabetic and Retinal Vascular Eye Disease

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KEYWORDS

• Diabetic retinopathy • Diabetic macular edema • Retinal vascular disease
• Retinal vein occlusion • Retinal artery occlusion

KEY POINTS

- Diabetic retinopathy is the leading cause of blindness in working-age adults.
- Blood glucose and blood pressure control can lower the risk of diabetic retinopathy.
- Routine dilated ophthalmologic examinations can aid in earlier recognition and treatment of diabetic retinopathy and reduce the risk of vision loss. Telemedicine can facilitate easier access to diabetic retinopathy screening.
- Retinal vein occlusion in patients younger than age 50 and in those without known vascular risk factors should prompt further workup for underlying systemic disorders.
- Patients presenting with acute painless vision loss concerning for retinal artery occlusion require emergent stroke workup.

DIABETIC RETINOPATHY

How Common Is Diabetic Retinopathy?

Diabetic retinopathy, a microvascular complication of diabetes mellitus, is the leading cause of blindness worldwide among patients aged 25 to 75.[1] It occurs in both type 1 and type 2 diabetes. Diabetes affected 463 million people in 2019, and its prevalence is expected to increase to 700 million by 2040.[2] About one-third of patients with diabetes have diabetic retinopathy, and 1 in 10 patients will develop vision-threatening disease.[3,4] In the United States alone, approximately 1 in 10 people have diabetes.[5] In 2010, approximately 7.7 million Americans had diabetic retinopathy, and this number is projected to double to 14.6 million by 2050.[6]

The prevalence of diabetic retinopathy increases with the duration of diabetes. After 20 years of living with diabetes, approximately 99% of patients with type 1 diabetes and 60% of patients with type 2 diabetes develop some form of diabetic retinopathy.[7]

The Diabetes Control and Complications Trial (DCCT)[8] and United Kingdom Prospective Diabetes Study (UKPDS),[9] both randomized clinical trials, have shown that intensive glycemic control reduces diabetic complications, including retinopathy, in both type 1 and type 2 diabetes.

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How Does Diabetes Cause Damage to the Retina?

Diabetic retinopathy occurs because of damage to retinal capillaries caused by prolonged exposure to hyperglycemia.[10] Although not yet well-delineated, the pathophysiology is thought to involve several biochemical reactions, including increases in inflammatory oxidative stress, advanced glycation end products, and protein kinase C pathways. The net effect results in endothelial damage, basement membrane thickening, and pericyte loss. Over time, damage to retinal capillaries leads to capillary occlusion and retinal ischemia. In addition, the compromised endothelial barrier leads to serum leakage and retinal edema. In late-stage retinopathy, ischemic retinal tissue produces intraocular vascular endothelial growth factor (VEGF), which promotes intraocular neovascularization. These abnormal blood vessels are fragile and can bleed within the eye, causing vision loss and elevated intraocular pressure. When regressed, the fibrotic neovascular remnants can exert traction on the retina, leading to retinal detachment.

How Is Diabetic Retinopathy Staged?

Diabetic retinopathy is staged on a severity scale based on clinical features seen on dilated fundus examination.[11] Ophthalmologists first classify disease as either nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR). The key difference between NPDR and PDR is the presence of neovascularization in PDR.

NPDR is graded as mild, moderate, severe, or very severe depending on the observed intraretinal pathology, including microaneurysms, intraretinal hemorrhages, venous beading, and intraretinal microvascular abnormalities (**Fig. 1**). Proliferative diabetic retinopathy is graded non-high-risk versus high-risk. Non-high-risk PDR may have mild neovascularization of the optic nerve head and/or neovascularization elsewhere in the retina but does not have vitreous hemorrhage (**Fig. 2**). High-risk PDR is characterized by moderate to severe neovascularization of the optic nerve head or neovascularization elsewhere in the retina with vitreous hemorrhage (**Fig. 3**). Diabetic macular edema (DME), which is swelling of the central retina, may occur at any stage of retinopathy. Proper documentation of a diabetic eye examination requires both grading of retinopathy and description of DME.

Higher levels of glycosylated hemoglobin (HbA1c) correlate with the progression of retinopathy from mild NPDR to high-risk PDR.[12] Patients with severe NPDR have a 15% risk of progression to high-risk PDR within 1 year. The risk is increased to

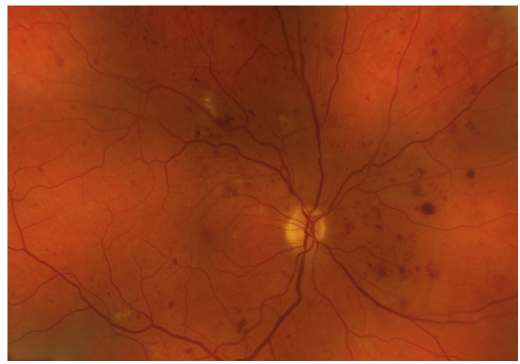

Fig. 1. Severe NPDR. Fundus photograph of the right eye shows diffuse microaneurysms and intraretinal hemorrhages in all 4 quadrants.

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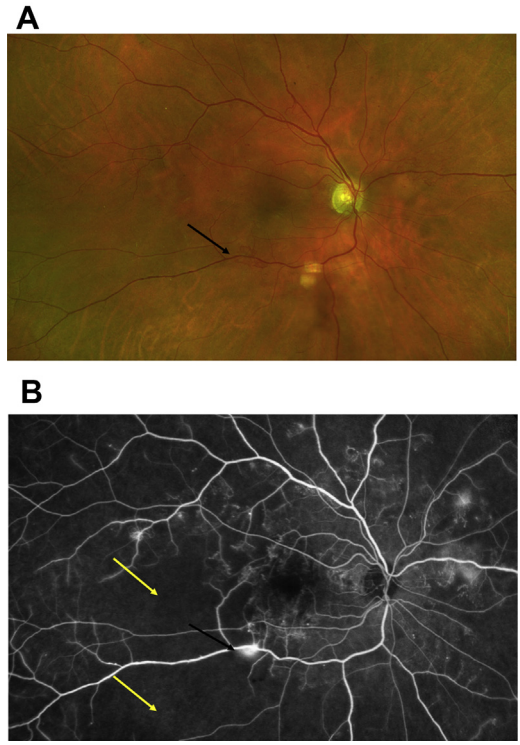

Fig. 2. Non-high-risk PDR. (*A*) Fundus photograph of the right eye shows a net of neovascularization along the inferior vascular arcade (*black arrow*). (*B*) Fluorescein angiogram demonstrates neovascularization and areas of nonperfusion (*yellow arrows*). Note that there is no neovascularization of the optic nerve head and no vitreous hemorrhage.

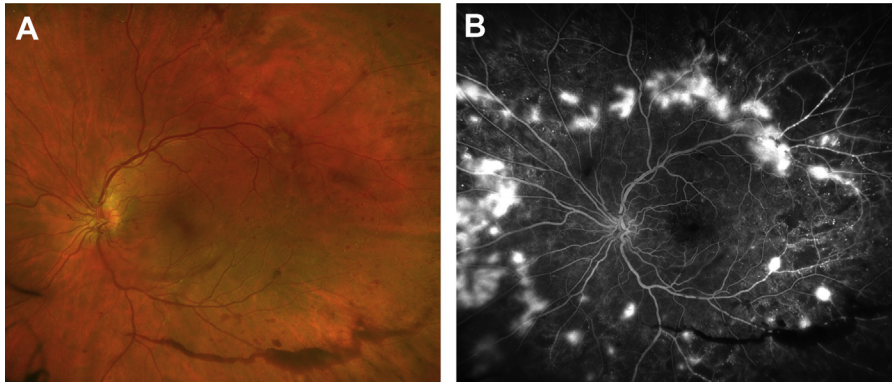

Fig. 3. High-risk PDR with vitreous hemorrhage. (*A*) Fundus photograph of the left eye shows neovascularization along the superior vascular arcade and vitreous hemorrhage settling inferiorly. (*B*) Fluorescein angiogram reveals more extensive neovascularization and multiple areas of non-perfusion.

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45% for those with very severe NPDR.[13] Patients with NPDR are therefore monitored at different follow-up intervals depending on their disease severity. No ophthalmic treatment is absolutely indicated unless visually significant diabetic macular edema is present. Patients should be educated on the importance of systemic management including blood glucose and blood pressure control to lower the risk of retinopathy progression.[14] The DCCT showed that intensive glycemic control reduced the risk by 34% to 76% over the entire spectrum of retinopathy, thereby reducing the need for laser treatment and loss of vision.[8,15] Tight glycemic control remains the most critical and most effective strategy for preventing vision loss from diabetic retinopathy.

Patients with PDR, especially those with high-risk features, are treated with panretinal photocoagulation (PRP).[16] This treatment destroys the ischemic retina to minimize production of VEGF, thereby preventing neovascularization. Intravitreal anti-VEGF agents are also used alone or in combination with PRP to control neovascularization.[17] It is recommended that patients with limited ability for close follow-up receive PRP instead of anti-VEGF monotherapy, as the latter is shorter-acting, more costly, and requires repeated treatments for effect. Prophylactic PRP has also been recommended for patients with very severe NPDR who are at high risk for progression and/or have difficulty with routine follow-up.[13]

When and How Often Should Patients with Diabetes Be Screened?

Screening recommendations vary depending on the types of diabetes, and on whether or not the patient is pregnant (**Table 1**).[11] Diabetic retinopathy is rare within the first 5 years following the diagnosis of type 1 diabetes mellitus. In contrast, a significant percentage of patients with type 2 diabetes already have retinopathy at the time of initial diagnosis. The recommended time of first dilated eye examination is thus 5 years after diagnosis for patients with type 1 diabetes, and immediately at diagnosis for patients with type 2 diabetes. Pregnancy increases the risk of progression of diabetic retinopathy—thus, pregnant women with any type of diabetes should have a dilated eye examination early in the first trimester and frequent follow-up. According to the Diabetes Report Card 2017, the dilated eye examination is one of the key preventative care practices that help patients better manage their condition and improve their health.[18] Several level 1, randomized, controlled studies[13,16,19] demonstrate the effectiveness of timely treatment in reducing the rate and severity of vision loss from diabetic retinopathy. It is therefore critical that patients with diabetes receive routine dilated eye examinations, which are necessary to detect complications of diabetic retinopathy.

Over the past decade, the use of nonmydriatic cameras for retinal imaging, combined with the remote evaluation of images at a telemedicine reading center, has

Table 1
Dilated eye examination schedule for patients with diabetes mellitus

Diabetes Type	Initial Evaluation	Follow-up
Type 1	5 years after diagnosis	Annually
Type 2	At time of diagnosis	Annually
Pregnancy with type 1 or type 2	Soon after conception and early in the first trimester	Every 3 months

Modified from American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco: American Academy of Ophthalmology; 2019. Available at www.aao.org/ppp.

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been utilized for diabetic retinopathy screening.[20] Such strategies implemented in primary care settings have been shown to increase screening rates among patients with diabetes, including those who are at high risk of missing recommended eye examinations.[21,22] Currently, an estimated one-third of adults with diabetes in the United States do not receive an annual dilated eye examination. Because most patients with diabetes have regular contact with primary care physicians, telemedicine screening in primary care and/or a medical subspecialist's office has immense potential to provide convenient and timely diabetic retinopathy screening to many patients.[23] Telemedicine diabetic retinopathy screening programs also have the collateral benefit of detecting other ocular conditions including cataract, hypertensive retinopathy, glaucoma, and age-related macular degeneration.[20]

When and How Often Should Patients with Diabetic Retinopathy See a Retina Specialist?

An optometrist or a general ophthalmologist can perform the initial screening examination. Depending on the severity of disease, the patient may then be referred to a retina specialist for further evaluation. In addition to a dilated fundus examination, patients may undergo ancillary studies including optical coherence tomography (OCT) imaging and fluorescein angiogram (FA) to better evaluate the retinopathy. The follow-up interval is dictated by the disease severity and by the presence and type of DME, which can occur at any stage of retinopathy (**Table 2**).[11] Nonpregnant patients with diabetes should have a dilated eye examination at least once per year and as often as every 1 to 6 months depending on disease severity. Patients with DME affecting the center of their vision, for example, may even require monthly evaluation for intravitreal injections. In general, any patient with proliferative diabetic retinopathy and/or visually significant diabetic macular edema requires the care of a retinal specialist.

Table 2
Dilated eye examination schedule for patients with diabetic retinopathy with or without diabetic macular edema

	Follow-up (months)		
Diabetic Retinopathy Severity	**No DME**	**NCI DME**	**CI DME**
Mild NPDR	12	4–6	1
Moderate NPDR	6–12	3–6	1
Severe NPDR	4	2–4	1
PDR	4	2–4	1

Abbreviations: CI DME, center-involved diabetic macular edema; DME, diabetic macular edema; NCI DME, non– center-involved diabetic macular edema; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Modified from American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco: American Academy of Ophthalmology; 2019. Available at www.aao.org/ppp.

How Does Diabetic Retinopathy Cause Vision Loss?

In the early stages of diabetic retinopathy, especially in the absence of macular edema, patients are often asymptomatic. In the late stages, it is common for patients with poorly controlled diabetes to present with devastating vision loss caused by different manifestations of the disease.

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Patients with diabetic retinopathy can develop acute, subacute, or chronic vision loss by several mechanisms:

- Capillary leakage → diabetic macular edema
- Capillary occlusion → macular ischemia → macular atrophy
- Sequela of ischemia-induced neovascularization, including vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma

Capillary leakage causes diabetic macular edema. Capillary occlusion involving the central retina can lead to ischemic maculopathy. Longstanding and severe disease can lead to vision-threatening conditions including macular atrophy and complications from ischemia-induced neovascularization: vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma.

Diabetic macular edema

DME is caused by capillary leakage in the setting of a decompensated endothelial barrier of the retinal vasculature. Higher HbA1c levels are associated with increased risk of developing and progressing DME.[24] Poorly controlled hypertension also contributes to worsening of DME.[9]

DME can occur at any stage of diabetic retinopathy and is classified based on whether or not the edema involves the center of the retina (the fovea) as seen on OCT imaging (**Fig. 4**). Center-involved (CI-DME) portends a worse prognosis compared with non-centered-involved DME (NCI-DME), as the risk of visual loss is greater if the swelling is at the fovea. Thus, patients with CI-DME are recommended to have more frequent follow-up.

It is important to note, however, that the amount of edema does not always correlate with the degree of vision loss. Many patients can be asymptomatic with good visual

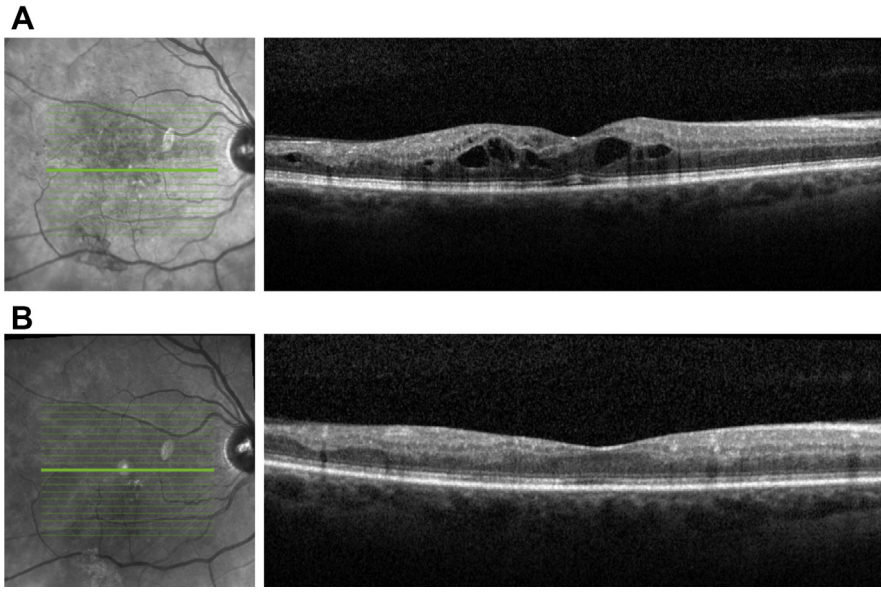

Fig. 4. DME. (*A*) Optical coherence tomography (OCT) image shows center-involved DME in the right eye. (*B*) Resolution of DME after treatment with intravitreal aflibercept (Eylea) in the same eye.

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acuity despite the presence of CI-DME. Education on blood sugar control and close monitoring is appropriate for these patients.

Patients with visually significant DME can be treated with intravitreal anti-VEGF, intravitreal corticosteroids, and/or focal laser photocoagulation. Intravitreal anti-VEGF agents are currently the first line therapy, and include bevacizumab (Avastin), aflibercept (Eylea), and ranibizumab (Lucentis).[25] Of note, glitazone class of oral anti-hyperglycemic agents such as rosiglitazone and pioglitazone should be used with caution in patients with DME, as these agents have been associated with development or worsening of macular edema.[26]

Ischemic maculopathy

Hyperglycemia-induced microvascular damages lead to retinal capillary occlusion and retinal ischemia. If this occurs in the central retina, patients develop gradual and permanent vision loss. Although other causes of vision loss in diabetic eyes such as macular edema, vitreous hemorrhage, or retinal detachment can be seen on dilated fundus examination, the diagnosis of macular ischemia often requires ophthalmic imaging.[27] Macular ischemia can be visualized on OCT angiogram or fluorescein angiogram as an enlarged foveal avascular zone (**Fig. 5**). Over time, an ischemic macula can become atrophic. On OCT, the retina appears thin with loss of photoreceptors and attenuation of retinal layers (**Fig. 6**).

Vitreous hemorrhage

Vitreous hemorrhage is a potential complication of proliferative diabetic retinopathy characterized by intraocular bleeding within the vitreous cavity (**Fig. 7**). The up-regulation of VEGF induced by retinal ischemia leads to the growth of abnormal blood vessels. These vessels are friable and prone to spontaneous bleeding. Patients may present with symptoms ranging from mild blurry vision to sudden, severe vision loss. Patients also frequently describe increased floaters, a hazy hue in vision, or dark strands in their field of vision. These symptoms are caused by the diffuse red blood cells or blood clots that adhere to vitreous strands. Diabetic retinopathy is the most common underlying etiology in adults presenting with vitreous hemorrhage.

When a patient presents with vitreous hemorrhage, the most important first step of the management is to rule out the presence of retinal tear and/or retinal detachment. If the vitreous hemorrhage is severe enough to obscure the view to the retina, then

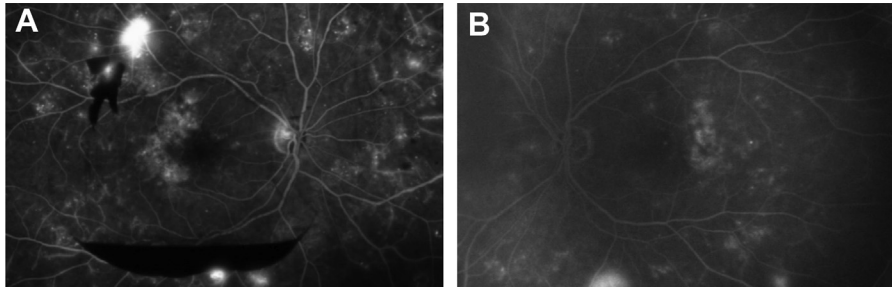

Fig. 5. Macular ischemia. (*A*) Fluorescein angiogram of the right eye with proliferative diabetic retinopathy demonstrates capillary nonperfusion in the center of the macula and thus an enlarged foveal avascular zone compared to that of the contralateral eye of the same patient. There is also capillary leakage, neovascularization, and preretinal hemorrhage. (*B*) Fluorescein angiogram of the left eye is notable for microaneurysms, capillary leakage, and neovascularization.

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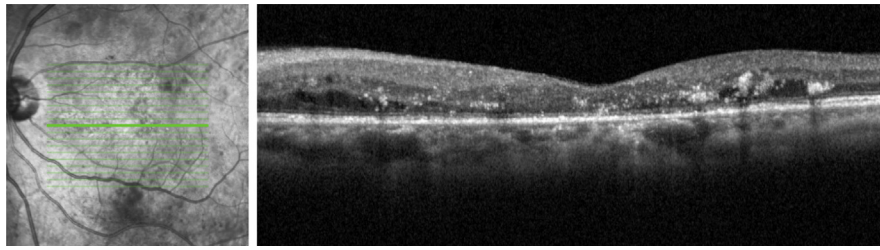

Fig. 6. Macular atrophy. Optical coherence tomography (OCT) image of the left eye shows central thinning of the retina and attenuation of the outer retinal layers.

ocular ultrasound is indicated to rule out retinal detachment. Immediate treatment options include anti-VEGF and/or laser photocoagulation if possible. Importantly, vitreous hemorrhage is not a contraindication to continuing systemic anticoagulant medications (such as aspirin, clopidogrel, or coumadin) that are indicated for other medical reasons.[28] Patients should avoid nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen if possible. Pars plana vitrectomy with endolaser is the treatment for nonclearing vitreous hemorrhage. Early surgical intervention has been shown to improve visual outcomes in patients with type 1 diabetes, but not type 2 diabetes.[29]

Retinal detachment

Patients with proliferative diabetic retinopathy are also at increased risk of vision loss from retinal detachment. When retinal neovascularization extends into the vitreous and proliferates into fibrovascular tissues, the resulting traction can cause retinal detachment (**Fig. 8**). If this complication occurs outside of the macula, the patient may remain asymptomatic for many years. If retinal detachment involves or threatens the macula, patients will develop vision loss and may describe photopsia because of traction exerted on the retina. Prompt surgical intervention with vitrectomy and removal of proliferative tissues is then indicated. Contraction of the fibrovascular tissues may cause a retinal break, leading to a combined tractional and rhegmatogenous

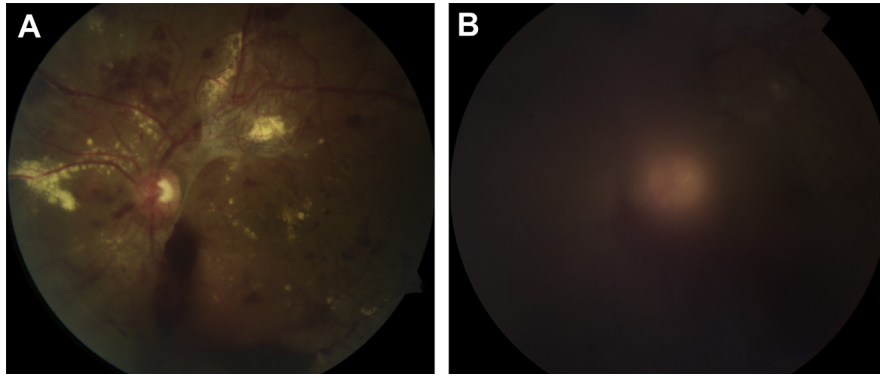

Fig. 7. Vitreous hemorrhage. (*A*) Fundus photograph of an eye with mild vitreous hemorrhage, most of which has settled inferiorly. There is sufficient view to deliver laser photocoagulation in areas of the retina not obscured by blood. (*B*) Fundus photograph of a different eye with diffuse vitreous hemorrhage limiting visualization of the entire retina.

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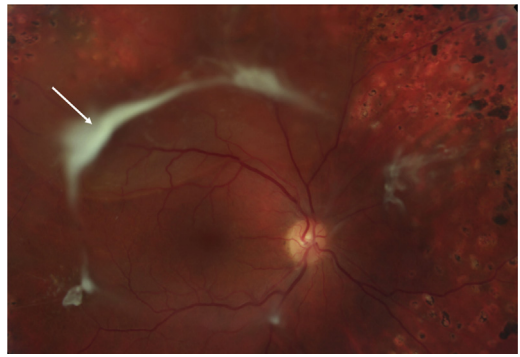

Fig. 8. Retinal detachment. Fundus photograph of the right eye shows fibrotic tissue (*arrow*) causing tractional retinal detachment that is threatening the macula.

retinal detachment. Urgent or emergent surgery is recommended for these patients. Patients frequently require placement of expansile gas or silicone oil in the eye as part of the operation. After surgery, patients are instructed to adhere to a certain position to optimize the chance of retina reattachment. If expansile gas is used, patients will be restricted from flying in airplanes or traveling over areas of high elevation such as mountains until the gas bubble is resorbed, which may take 3 to 8 weeks.[30] The use of nitrous oxide anesthesia in patients with intraocular gas is contraindicated as the mixture of gas and nitrous oxide can cause irreversible vision loss.[31]

Neovascular glaucoma

In the proliferative stage of diabetic retinopathy, neovascularization can also result in abnormal vessel growth on the iris and within the angle of the anterior chamber, leading to a form of angle closure glaucoma.[11] Patients with neovascular glaucoma often need urgent incisional surgery, in which a glaucoma drainage device is implanted into the eye to improve aqueous outflow. Left untreated, neovascular glaucoma can quickly result in a blind painful eye, for which enucleation is indicated.

What Else Can Look Like Diabetic Retinopathy?

Other retinal vascular diseases such as radiation retinopathy, sickle cell retinopathy (SCR), and hypertensive retinopathy can mimic diabetic retinopathy.

Exposure to ionizing radiation, either external beam or local plaque therapy, can damage the retina and cause microangiographic abnormalities similar to diabetic retinopathy. Fundus examination of radiation retinopathy shows cotton-wool spots, microaneurysms, retinal hemorrhages, macular edema, and neovascularization that are indistinguishable from diabetic retinopathy.[32] In suspected cases, it is important to elicit a history of radiation to differentiate the diagnoses.

SCR is caused by arteriolar and capillary occlusion. Like diabetic retinopathy, SCR is also classified as nonproliferative versus proliferative. Although sickle cell disease results in more systemic complications, proliferative SCR is more commonly associated with sickle cell hemoglobin C (Hb SC) and sickle cell thalassemia (SThal). Patients with SCR may lose vision because of macular ischemia, vitreous hemorrhage, and tractional retinal detachment.[33]

Hypertensive retinopathy can also feature similar retinal microvascular signs, which are predictive of incident stroke, congestive heart failure, and cardiovascular mortality.[34] Patients may present with acute bilateral blurry vision during a hypertensive crisis. Vision loss in this setting usually recovers with blood pressure control.

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How Else Does Diabetes Affect the Eye?

Diabetes can affect other structures of the eye apart from the retina, such as the cornea, the crystalline lens, and the cranial nerves. Thus, it is important for patients with diabetes to have a comprehensive eye evaluation in addition to the dilated fundus examination.

Diabetic neuropathy can affect cranial nerve V, causing corneal hypoesthesia or anesthesia, leading to neurotrophic keratopathy. This can present as persistent or recurrent corneal epithelial defects which may in turn increase the risk of corneal infection and perforation.[35] Patients with diabetes are at risk of poor healing after any ophthalmic surgery that involves the cornea such as cataract surgery or LASIK.[36]

Buildup of glucose in the aqueous humor and the crystalline lens can impair the lens' clarity, refractive index, and accommodative amplitude.[37] Patients with poorly controlled diabetes may therefore present with fluctuating blurry vision because of acute myopic shifts. Over time, prolonged hyperglycemia in the aqueous humor will also predispose patients to cataract formation. Patients with both type 1 and type 2 diabetes have a higher prevalence of cataracts than the general population. Patients with poorly controlled type 1 diabetes are at risk of subacute loss of vision in both eyes due to what are called bilateral snowflake cataracts. Patients with type 2 diabetes, on the other hand, develop typical age-related cataracts at a slightly earlier onset.[38]

Microvascular ischemia caused by diabetes can also manifest as cranial nerve vasculopathy, mostly commonly affecting cranial nerve VI. Patients present with double vision because of inability to abduct the affected eye. Diabetic ischemic cranial nerve palsies typically resolve within 4 to 6 months.[39]

Ischemia of cranial nerve II may present acutely as diabetic papillopathy, which may progress to optic atrophy in the late phase. Patients present with a pale optic nerve head, a relative afferent pupil defect, decreased vision, loss of color vision, and visual field loss. Unfortunately, there is no treatment for diabetic papillopathy or optic atrophy.[40]

OTHER RETINAL VASCULAR DISEASES

In addition to diabetic retinopathy, there are many other retinal vascular diseases that are associated with systemic conditions. This section discusses two entities that are commonly encountered in eye clinic: retinal vein occlusion (RVO) and retinal artery occlusion (RAO).

Retinal Vein Occlusion

RVO is the second leading cause of blindness from retinal vascular disease after diabetic retinopathy, and affects more than 16 million people worldwide.[41] RVO is further classified as central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) based on the location of the obstruction.

What causes central or branch retinal vein occlusion?

Both CRVO and BRVO are acute events caused by thrombus formation. In CRVO, a thrombus obstructs the central retinal vein, leading to vascular congestion, intraretinal hemorrhages, capillary nonperfusion, and capillary leakage. In BRVO, a branch retinal artery—thickened by arteriosclerosis—mechanically compresses a branch retinal vein at an arteriovenous crossing, leading to venous stasis and subsequent thrombus formation. The same downstream cascade of events resulting from vascular congestion then ensues, but the damage is isolated to the part of the retina being drained by the branch retinal vein.[42]

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Who gets central or branch retinal vein occlusion?

CRVO and BRVO classically present in elderly patients with vascular risk factors. The cumulative prevalence of RVOs of both types is about 0.5% in patients older than age 40. The Eye Disease Case-Control Study Group (EDDC) identified risks factors for CRVO and BRVO.[43,44] Systemic risk factors for CRVO include hypertension, diabetes, smoking, and age. Systemic risk factors for BRVO include hypertension, cardiovascular disease, increased body mass index before age 20, and hypercoagulopathy/hyperviscosity.

For patients older than age 50 presenting with RVO who have known vascular risk factors, further workup to rule out underlying systemic precipitants of the RVO is not necessary. For younger, healthy patients, and particularly those presenting with bilateral RVOs, an underlying hypercoagulopathy/hyperviscosity syndrome or systemic vasculitis should be ruled out. Potential etiologies for RVO caused by an underlying systemic disease include:

- Hyperviscosity syndromes, such as leukemia, polycythemia vera, Waldenstrom macroglobinemia, and multiple myeloma
- Hypercoagulopathy, including factor V Leiden mutation, protein C deficiency, protein S deficiency, anticardiolipin antibody, antiphospholipid antibody, homocystinuria, and prothrombin mutation
- Vasculitis, including lupus, sarcoid, syphilis, and Behcet's disease

How does central and branch retinal vein occlusion cause vision loss?

Patients with RVO often present with acute painless vision loss and require urgent evaluation to establish the diagnosis. The severity of vision loss depends on the degree of retinal ischemia and presence or absence of macular edema. In CRVO, dilated fundus examination typically shows diffuse intraretinal hemorrhages, cotton-wool spots, and diffuse engorged and tortuous veins (**Fig. 9**). Macular edema is often present.[45] Similar findings are seen in BRVO, although limited to one area of the retina (**Fig. 10**), and macular edema is present only in about half of these patients.[46]

Over time, retinal ischemia can lead to the development of neovascularization of the optic nerve head, retina, angle, and iris. Retinal ischemia is more severe in patients

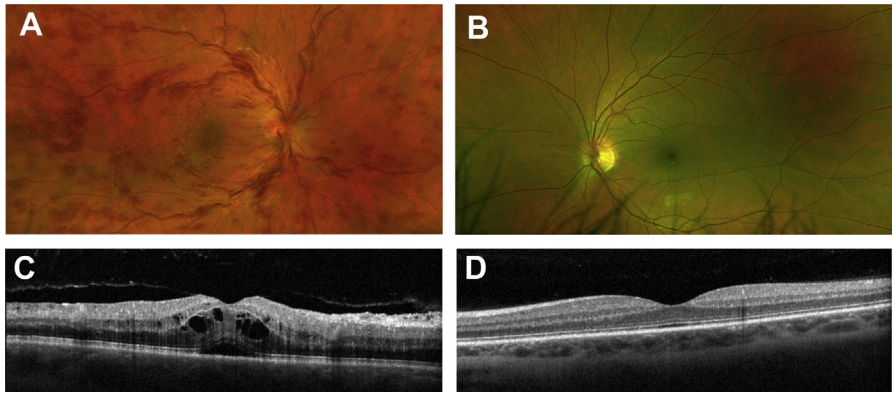

Fig. 9. CRVO. (*A*) Fundus photograph of the right eye shows diffuse intraretinal hemorrhages consistent an acute CRVO. (*B*) Fundus photograph of the unaffected left eye. (*C*) Optical coherence tomography (OCT) image shows macular edema, which may present in the acute phase of CRVO. (*D*) OCT image of the unaffected left eye with normal retina.

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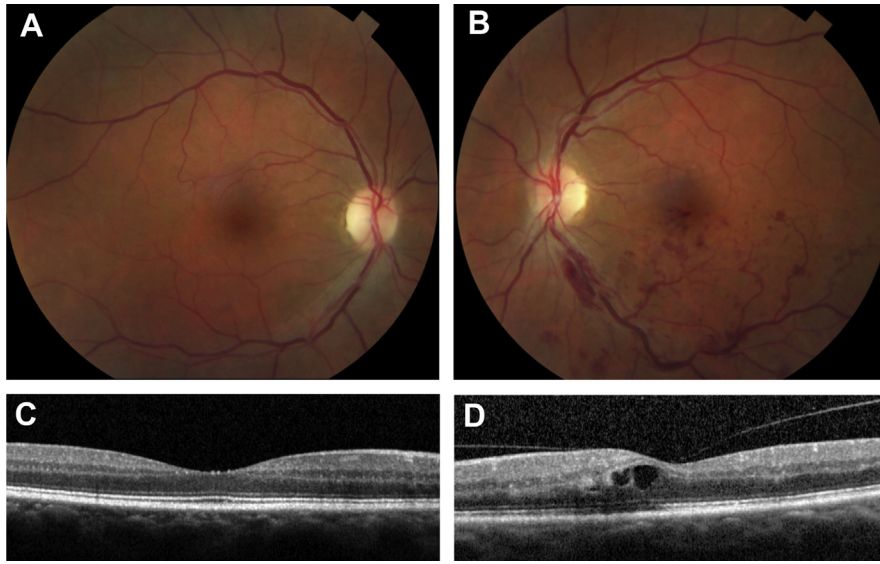

Fig. 10. BRVO. (*A*) Fundus photograph of the unaffected right eye. (*B*) Fundus photograph of the left eye with intraretinal hemorrhages in the inferior retina consistent with an inferior BRVO. (*C*) OCT image of the unaffected right eye with normal retina. (*D*) OCT image of the left eye with macula edema caused by BRVO.

with CRVO, who are more likely to develop complications from neovascularization. The presence of neovascularization is an indication for treatment with laser photocoagulation, as there are many potential vision-threatening complications from neovascularization (e.g., vitreous hemorrhage, retinal detachment, and neovascular glaucoma). In addition to neovascularization, both CRVO and BRVO may leave patients with chronic risk of recurrent macular edema requiring long-term management. The treatment for RVO-related macular edema is similar to treatment of diabetic macular edema, with anti-VEGF agents being first-line, followed by intravitreal corticosteroids and/or laser photocoagulation.[47,48]

Retinal Artery Occlusion

Retinal artery occlusion is a medical emergency wherein the central retinal artery delivering blood supply to the inner layers of the retina or any of its branch tributaries is obstructed.[49] Similar to retinal vein occlusion, the severity of retinal arterial occlusive disease depends on the vessel involved (i.e., whether the occlusion is of the central retinal artery or a branch retinal artery).

What causes central or branch retinal artery occlusion?

Both central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO) are caused by embolic and/or thrombotic occlusion. Retinal artery occlusion in patients of any age is often a sign of serious underlying systemic disease and should prompt a thorough evaluation. Older patients require evaluation for giant cell arteritis (GCA), as well as stroke workup including carotid ultrasound, echocardiogram, and brain imaging. A workup for hypercoagulopathy/hyperviscosity syndrome and/or vasculitis is recommended for afflicted younger patients.

Common causes of emboli associated with cardiovascular diseases include cholesterol emboli (i.e., Hollenhorst plaque) originating from the carotid arteries, platelet-fibrin

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emboli originating from atherosclerotic plaques, and calcific emboli originating from cardiac valves.
Other thromboembolic etiologies include:

- Fat emboli from long-bone fractures
- Septic emboli from infectious endocarditis
- Talc emboli from intravenous drug use
- Cardiac myxoma
- Arrhythmias
- Mitral valve prolapse
- Oral contraceptive use or pregnancy
- Coagulation disorders
- Sickle cell disease
- Retinal vasculitis
- Connective tissue disorders

How does central or branch retinal artery occlusion cause vision loss?
In CRAO, obstruction of the central retinal artery impairs blood flow to most of the retina, and patients present with sudden, severe, painless loss of vision. The ischemic retina becomes edematous and appears opaque. The orange-red color of the choroidal vasculature beneath the foveola produces the appearance of the classic cherry-red spot in the center of the opaque macula. In the acute phase, OCT imaging shows diffuse hyper-reflectivity and loss of internal layer definition (**Fig. 11**). The central retinal artery eventually recanalizes with resolution of retinal edema, but the vision loss persists as the retina becomes atrophic. Most patients have permanent vision deficits worse than 20/400.[50,51] If there is a patent cilioretinal artery, present in about 20% of the general population, the patient may have some degree of central vision.

In BRAO, the obstruction occurs at one of the branch retinal arteries, leading to edema and opacification of the inner retina in the distribution of the affected vessel (**Fig. 12**). Patients with BRAO present with a visual field defect, which will also remain permanent even once the occluded vessel recanalizes and the edema resolves. Because of retinal ischemia, patients with CRAO and BRAO are also at risk of neovascularization, although less so compared to those with retinal vein occlusions.[52,53] The presence of neovascularization should prompt consideration for combined artery and vein occlusion, ophthalmic artery occlusion, or ocular ischemic syndrome.

How are central and branch retinal artery occlusion managed?
Acute painless vision loss concerning for retinal artery occlusion requires immediate admission to an emergency department because of the high risk of ischemic stroke.[54] In particular, an elderly patient presenting with a CRAO needs emergent evaluation for GCA, which accounts for 1% to 2% of CRAO cases.[55] At minimum, serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and a complete blood count should be obtained. An elevated platelet count in the setting of elevated ESR and CRP is suggestive of GCA. In patients with suspected GCA, prompt initiation of high-dose systemic corticosteroids is recommended to prevent vision loss in the other eye.

Unfortunately, there are no proven treatments for vision loss caused by retinal artery occlusion. Potential treatments including ocular massage, anterior chamber paracentesis, hyperbaric oxygen therapy, and catheterization of the ophthalmic artery with tissue plasminogen activator have not been successful. Patients are monitored closely and treated with laser photocoagulation if they develop retinal or iris neovascularization.[49]

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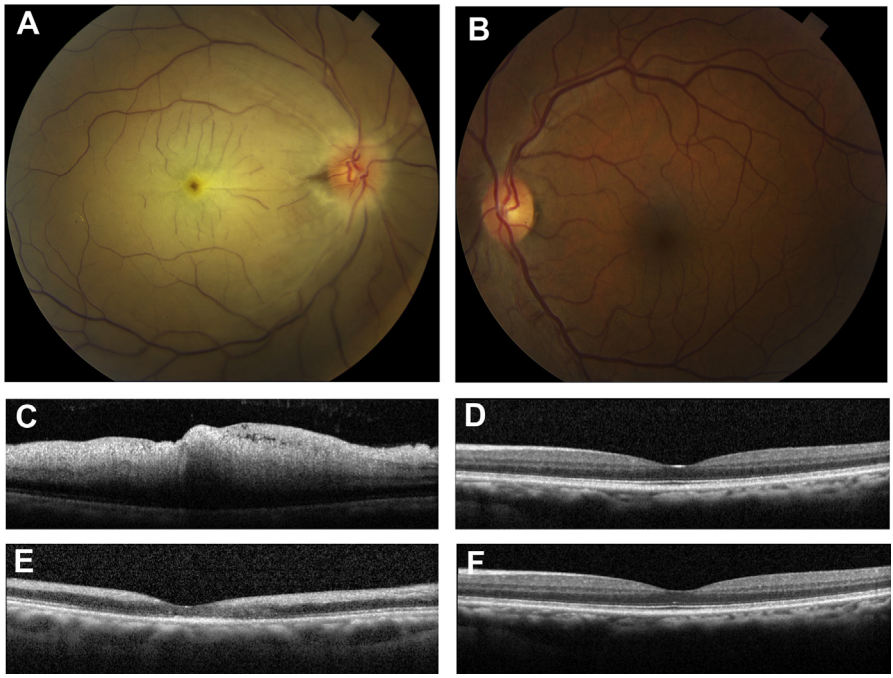

Fig. 11. CRAO. (*A*) Fundus photograph of the right eye shows diffuse retinal whitening and a cherry-red spot consistent with an acute CRAO. (*B*) Fundus photograph of the unaffected left eye. (*C*) OCT image of the right eye shows edema and opacification of the inner retinal layers during the acute phase of CRAO. (*E*) OCT image of the right eye shows thinning of the retina 6 weeks later in the late phase of the CRAO. (*D*, *F*) OCT images of the unaffected left eye with normal retina.

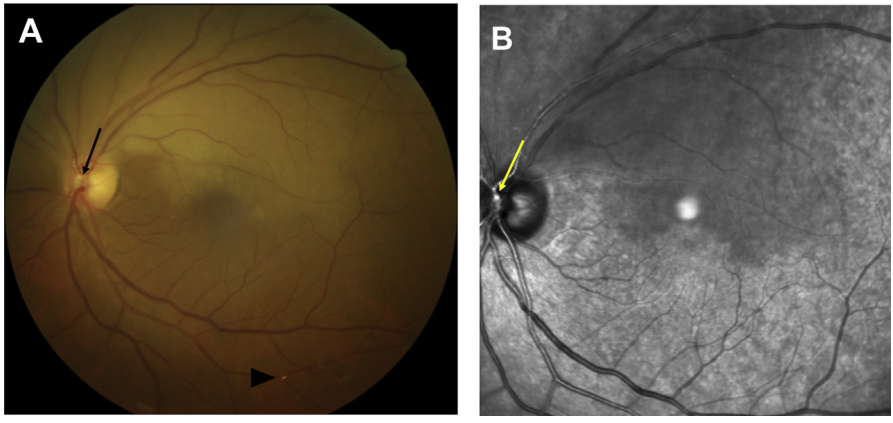

Fig. 12. BRAO. (*A*) Fundus photograph of the left eye shows segmental opacification of the retina consistent with a superior BRAO. In addition to the causative embolus seen near the branching point (*black arrow*), there is also a smaller embolus in the distal inferior vascular arcade (*arrowhead*). (*B*) Near-infrared reflectance imaging highlights the causative embolus near the branching point at the optic nerve head (*yellow arrow*).

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SUMMARY

The retinal vasculature is most commonly afflicted by uncontrolled diabetes but is also susceptible to thromboembolic insults associated with other systemic diseases. Both the internists and medical subspecialists play a crucial role in the prevention, detection, evaluation, and management of vision-threatening retinal vascular diseases.

CLINICS CARE POINTS

- Intensive glycemic control can prevent vision loss from diabetic retinopathy.
- Patients with diabetes who are pregnant require more frequent eye examinations.
- Regular dilated eye examinations by an ophthalmologist or via telemedicine screening offered by primary care physicians and/or medical subspecialists can provide convenient and timely diabetic retinopathy screening.
- For patients with diabetic retinopathy with poor access to follow-up care, early treatment with laser photocoagulation could be sight-saving.
- Systemic anticoagulants may be continued in patients with intraocular bleeding from diabetic retinopathy.
- Diabetic retinopathy can be mimicked by retinopathy caused by hypertension, radiation, and sickle cell disease.
- Patients with diabetes should be counseled that in addition to diabetic retinopathy, poorly controlled disease can also cause vision loss due to corneal ulceration, cataracts, cranial nerve palsy, and ischemic optic neuropathy.
- Retinal vein occlusion in young patients and in those without known vascular risk factors warrant a systemic work-up to identify potential underlying precipitants.
- Acute painless vision loss concerning for retinal artery occlusion requires immediate admission to an emergency department because of the high risk of ischemic stroke.
- Elderly patients presenting with retinal artery occlusion should be evaluated for GCA in addition to emergent stroke workup.

DISCLOSURE

The authors have nothing to disclose.

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