

Ocular Associations of Diabetes Other Than Diabetic Retinopathy

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Diabetic retinopathy is the most well-known ocular complication of diabetes and the leading cause of blindness among people 20–64 years of age in the U.S. (1). Up to 4 million Americans with diabetes, 40 years of age and older, have retinopathy, and nearly 1 million have sight-threatening retinopathy (2). In major clinical trials, tight control of blood glucose and blood pressure has been demonstrated to reduce the risk of retinopathy and associated blindness (3).

A range of ocular diseases is also associated with diabetes, which may lead to vision loss. However, some of these ocular conditions may not be familiar to noneye clinicians (4–6). In this review, we aim to highlight the frequencies, clinical presentations, natural histories, and management of these ocular conditions. Physicians who manage patients with diabetes may benefit from knowledge of these associated conditions and are thus able to ensure adequate and timely referral and treatment. Routine eye screening for retinopathy of individuals with diabetes offers the opportunity to detect these other ocular diseases early, many of which are sight threatening. Physician education remains an important public health strategy in the prevention of vision loss in patients with diabetes.

OCULAR CONDITIONS DIRECTLY ASSOCIATED WITH DIABETES

1. Cataracts and cataract surgery

Cataract is a major cause of vision impairment in people with diabetes. Numerous

studies have documented an association between diabetes and cataracts. This association is supported by an abundance of data from clinical epidemiological studies and basic science studies (7–22). Both cross-sectional and prospective data from three population-based studies, the Beaver Dam Eye Study, the Blue Mountains Eye Study, and the Visual Impairment Project, have documented associations between diabetes and both prevalent and incident posterior subcapsular cataract and, less consistently, with prevalent and incident cortical cataracts but not nuclear cataract (8–12,14–19,23,25). The Blue Mountains Eye Study showed that impaired fasting glucose, in the absence of clinical diabetes, was also a risk factor for the development of cortical cataract (7). There is additional evidence that the risk of cataract increases with increasing diabetes duration and severity of hyperglycemia (26). Deposition of advanced glycation end products in the lens has been postulated as one possible pathogenic mechanism for diabetic cataract (27).

Cataract surgery is the standard treatment for patients with cataract and significant vision impairment. In individuals with diabetes, cataract occurs at a younger age and progresses more rapidly, resulting in higher rates of cataract surgery at a relatively young age (28). In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the 10-year cumulative incidence of cataract surgery was 8% in those with type 1 diabetes and 25% in those with type 2 diabetes. Predictors of cataract surgery included older age,

greater severity of diabetic retinopathy, and baseline proteinuria in type 1 diabetes and older age and use of insulin in type 2 diabetes (25).

While the overall outcomes of cataract surgery are excellent, patients with diabetes may have poorer vision outcomes than those without diabetes, and the worst outcomes may occur in operated eyes with active proliferative retinopathy (29) and/or preexisting macular edema. To improve cataract surgical outcomes in patients with diabetes, adequate control of diabetic retinopathy with laser treatment before cataract surgery is necessary (30).

The most devastating postoperative complication is endophthalmitis, a severe intraocular infection, with several studies showing that patients with diabetes have an increased risk of developing this complication (31–34), resulting in poorer outcomes (35). Patients with endophthalmitis characteristically present with pain, redness, discharge, decreased vision, eyelid edema, proptosis, and conjunctival injection, with anterior chamber inflammation and vitritis. Management of endophthalmitis consists of inpatient admission for a combination of intravitreal, subconjunctival, and topical antibiotics and steroids and possibly ocular surgery. In patients with diabetes, treatment may need to be more aggressive, with surgery performed earlier rather than later (35).

2. Anterior ischemic optic neuropathy

Anterior ischemic optic neuropathy (AION) is an acute vascular condition of the optic nerve. Studies suggest that up to 25% of patients with AION have a history of diabetes (36). In patients with diabetes, diabetic microvascular disease affecting the anterior part of the optic nerve is thought to cause the ischemia (37, 38).

The optic disc in the contra-lateral eye of patients with AION is typically small in diameter with a small or absent cup, referred to as a “disc at risk.” Patients with AION usually present with moderate loss of vision upon awakening, presumably related to nocturnal systemic hypotension (39). Visual acuity is better than 20/200 in 60% of cases at presentation (40). Untreated, AION generally remains

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stable, and recurrence in the same eye is unusual (41). Good recovery of vision was observed in 43% of patients in the Ischemic Optic Neuropathy Decompression Trial (42).

There are no proven treatments for AION, and the Ischemic Optic Neuropathy Decompression Trial revealed no benefit of optic nerve decompression surgery (43). Currently, neuroprotective agents are being investigated for nonarteritic AION (NAION) and appear to be beneficial against secondary neuronal degeneration in animal models of ischemic retinal ganglion cell damage and optic nerve crush injury (44). There is no proven prophylaxis for AION, and the evidence for the efficacy of aspirin therapy is limited (45).

3. Diabetic papillopathy

Diabetic papillopathy is an uncommon optic nerve condition characterized by acute disc edema and mild vision loss (46). Diabetic papillopathy is a risk factor for the progression of diabetic retinopathy (47); and, in rare instances, papillopathy can precede the development of AION (48). Early investigators postulated a toxic effect of abnormal glucose metabolism on the optic nerve in individuals with diabetes; subsequent studies have suggested that diabetic papillopathy may be a mild and reversible form of AION (49).

The significance of this condition is twofold. First, this condition may be misdiagnosed as papilledema (50). Second, telangiectasia at the optic disc in diabetic papillopathy may be mistaken as neovascularization in the optic disc as part of proliferative diabetic retinopathy, leading to unnecessary laser photocoagulation. Diabetic papillopathy spontaneously improves within a year, and vision prognosis is usually good. In most patients, vision recovers to a level $\geq 20/30$ (51). Tightening diabetes control and treating coexistent hypertension and renal dysfunction may help with resolution of this condition. There is anecdotal evidence that intraocular steroid injection may benefit patients with vision impairment (52).

4. Ocular movement disorders

Extraocular motility disorders may occur in patients with diabetes, secondary to diabetic neuropathy, involving the third, fourth, or sixth cranial nerve. Rarely, simultaneous palsies of multiple extraocular nerves can occur (53,54). Diabetes is the underlying cause in 25–30% of pa-

tients aged 45 years and older who develop acute extraocular muscle palsy (55). In one study (56), 1% of patients with diabetes were found to have cranial nerve palsies, compared with only 0.13% of control subjects. Of these cases, 41% had a third nerve palsy. In another population-based study, patients with sixth cranial nerve palsy were six times more likely to have diabetes (57).

Patients with extraocular palsies present with binocular diplopia. Pupil sparing is an important diagnostic feature in diabetes-related third cranial nerve palsy, distinguishing it from surgical causes, such as intracranial aneurysm or tumor. In diabetic cranial nerve palsies, recovery of extraocular muscle function generally occurs within 3 months (58). Recurrences can be common and may involve the same or other cranial nerves. The presence of other focal neurological signs, progressive deterioration, or palsy in a patient younger than 45 years should be investigated to exclude a compressive lesion. In these instances, a neurology or neuro-ophthalmology consultation is recommended.

OCULAR CONDITIONS FOR WHICH DIABETES IS A KNOWN RISK FACTOR

1. Glaucoma

Glaucoma is a progressive optic neuropathy associated with typical optic disc changes and visual field defects. Elevated intraocular pressure is the major risk factor for glaucoma, although a proportion of patients with glaucoma do not have raised intraocular pressure. Patients with diabetes are at risk of two major types of glaucoma: primary glaucoma and neovascular glaucoma.

a. Primary glaucoma. Several large epidemiological studies have reported positive associations between diabetes with primary open angle glaucoma (POAG), the most common form of primary glaucoma, or elevated intraocular pressure in the absence of glaucoma optic neuropathy (59–63). Glaucoma occurs more often in patients with diabetes (5%) than in the general population (2%) (64). The risk of glaucoma has been reported to be 1.6–4.7 times higher in individuals with diabetes than in nondiabetic individuals (65–68). In the Blue Mountains and Beaver Dam Eye studies, participants with diabetes were twice as likely to have

glaucoma as those without. However, not all population-based studies have identified such an association (69–73).

There are clear biologically plausible mechanisms supporting an association between diabetes and POAG. First, microvascular damage from diabetes could impair blood flow to the anterior optic nerve, resulting in optic nerve damage (37,38). Diabetes also impairs the auto-regulation of posterior ciliary circulation, which may exacerbate glaucomatous optic neuropathy (74). Second, patients with diabetes often have concomitant cardiovascular risk factors (e.g., hypertension) that may affect vascular perfusion of the optic nerve head (75). Finally, relative to those without diabetes, individuals with diabetes may be more vulnerable to elevated intraocular pressure (76), with more severe visual field loss at the same intraocular pressure level (77).

It is important to screen for POAG among individuals with diabetes, as POAG can be asymptomatic until the late stages, when decreased vision and/or constricted visual fields are noted. Treatment involves lowering intraocular pressure through topical eye drops and laser and surgical procedures. Primary angle closure glaucoma (PACG), the other common primary glaucoma, is characterized by narrow or closed anterior chamber angles, which impedes drainage of aqueous humor and leads to raised intraocular pressure. Patients with PACG appear to be more likely to have abnormal glucose tolerance than those with POAG or those without glaucoma (78). Diabetes may be associated with PACG via systemic autonomic dysfunction or increased lens thickness as a result of sorbitol overload (79,80). Patients with PACG may present with an acute attack, which is associated with severe ocular pain, headaches, and nausea, with substantially elevated intraocular pressure. Acute PACG requires urgent referral and treatment.

b. Neovascular glaucoma. Studies have shown a consistent association between diabetes and neovascular glaucoma (81), with proliferative retinopathy the leading cause of this type of secondary glaucoma. Between 32 and 43% of neovascular glaucoma cases are caused by proliferative diabetic retinopathy (82,83). Neovascularization of the iris, an early precursor of neovascular glaucoma, is commonly seen in patients with long-standing poorly controlled diabetes (84). Hypoxia in the retina and other ocular tissue causes an increased expression of vascular endothe-

lial growth factor (VEGF), which stimulates new vessel formation in the iris (85) or in the anterior chamber angle (86). Neovascular glaucoma requires aggressive intervention to lower intraocular pressure with medication, followed by surgery (87). Regression of neovascularization following pan-retinal laser photocoagulation can occur if treated early (37,38).

2. Ocular ischemic syndrome

Ocular ischemic syndrome (OIS) is an uncommon vascular problem that results from chronic hypo-perfusion of the eye, most commonly caused by ipsilateral internal carotid or ophthalmic artery occlusion (88). Patients with OIS typically present with vision loss and dull ocular pain (87). The prevalence of diabetes in patients with OIS is higher than in the general population (69), with one study reporting that more than 50% of patients with OIS have diabetes (89). Diabetes is a major risk factor for carotid artery stenosis and plaque formation, the underlying causes of OIS (90).

The 5-year mortality rate among patients with OIS has been reported to be 40% or higher (91). Coexisting cardiovascular and cerebrovascular diseases are the main causes of death. Carotid ultrasonography is useful to delineate the presence and severity of carotid artery stenosis. Although carotid endarterectomy lowers the risk of stroke in patients with symptomatic carotid stenosis (92), it is unclear whether this procedure alters vision prognosis in eyes with OIS (93,94). The coexistence of diabetes with OIS may be an indicator of poorer vision prognosis, due to the higher incidence of secondary glaucoma (94). Pan-retinal laser photocoagulation is indicated in eyes with ocular neovascularization.

OCULAR CONDITIONS WHERE DIABETES IS A POSSIBLE RISK FACTOR

1. Retinal vein occlusion

Retinal vein occlusion (RVO) is a retinal vascular condition characterized by dilated tortuous retinal veins with retinal hemorrhages, cotton wool spots, and macular edema. Central RVO occurs at the optic disc (95), whereas branch RVO occurs at retinal venular branches, usually at the site of arterio-venous crossing (96). Central RVO may be subdivided further into nonischemic and ischemic types, the latter associated with poorer vi-

sion prognosis (97). Although it has been thought that diabetes is a major risk factor for RVO, epidemiological studies have not shown a consistent relationship between diabetes and the presence of RVO, with some studies reporting a positive association (98–102) and others finding no association (103–106). The importance of RVO in patients with diabetes is that the retinal signs (e.g., hemorrhages or cotton wool spots) may “mimic” diabetic retinopathy. Thus, when patients with diabetes present with acute vision loss and asymmetric signs of “diabetic” retinopathy, RVO should be considered.

The management of RVO depends upon the site of occlusion (central or branch), degree of ischemia, presence of macular edema, visual acuity level, and complications. Approximately 30% of central RVO cases are initially nonischemic, but ~10% progress to ischemia within 6 months (107). The two major complications of RVO are secondary neovascular glaucoma and macular edema. Pan-retinal laser photocoagulation has been shown to prevent neovascular glaucoma (108). No treatment has proven effective for macular edema in patients with central RVO, although focal laser treatment may be useful in patients with macular edema and branch RVO (109). Clinical trials are on-going to assess the intraocular administration of pharmaceutical agents, such as steroids (110) or antivascular endothelial growth factor agents (111,112).

The vision prognosis with central RVO, particularly ischemic central RVO, is poor, but that of branch RVO is relatively good, with nearly half of patients maintaining visual acuity better than 20/40 (113). Patients with diabetes who develop RVO are more likely than their nondiabetic counterparts to develop retinal neovascularization (114), neovascular glaucoma, and vitreous hemorrhage (112). More importantly, recent studies suggest that, among those with diabetes 43–69 years of age, the presence of RVO is associated with double the risk of cardiovascular mortality (115).

Management of concomitant medical conditions (e.g., hypertension and dyslipidemia) may be important to prevent a recurrence of RVO (116). There is no good evidence that tight glycemic control can alter the course or improve the prognosis of RVO.

2. Retinal arteriolar emboli

Retinal arteriolar emboli are discrete plaque-like lesions lodged in the lumen of retinal arterioles. The majority of emboli are asymptomatic and transient, although patients infrequently present with episodes of sudden, painless, monocular blindness (amaurosis fugax), a transient ischemic attack, or stroke (117).

Population-based studies show that asymptomatic retinal emboli occur in 1.3–1.4% of adults 40 years of age and older (61,118). Studies show that retinal arteriolar emboli are associated with carotid artery disease, hypertension, other cardiovascular risk factors (117), and an increased risk of stroke and stroke-related (119,120) and all-cause (121) mortality. However, there are no consistent data on whether retinal arteriolar emboli occur more commonly in people with diabetes. In the Beaver Dam Eye Study, participants with type 2 diabetes were found to have a twofold higher prevalence of retinal emboli (60), but two other population-based studies have failed to confirm this association (61,105).

Once an embolus has been detected, a full cardiovascular and cerebrovascular risk assessment is recommended, including carotid artery ultrasound and echocardiography to assess the source of the emboli. Treatment of concomitant cardiovascular risk factors is vital and should include improved control of hyperglycemia, hypertension, and hyperlipidemia, cessation of smoking, and carotid endarterectomy, if indicated. Low-dose aspirin can be recommended to prevent retinal artery occlusion (122).

3. Retinal artery occlusion

Retinal artery occlusion (RAO) is a retinal vascular condition similar to emboli. The hallmark of RAO is sudden, unilateral, painless loss of vision associated with a visual field defect. Patients with central RAO usually present with a dramatic loss of vision, an afferent pupillary defect, diffuse retinal whitening, and the resultant classic “cherry spot” on the macula. The fundoscopic findings with branch RAO, which occur at a branch, usually consist of a focal wedge-shaped area of retinal whitening; vision loss also tends to be much milder. As for emboli, there is no clear evidence that patients with diabetes are at higher risk of RAO. However, the prevalence of diabetes among patients with RAO has been reported to be as high as 21%, which is higher than in the gen-

eral population of the same age (123,124).

Patients with RAO should be referred immediately to an ophthalmologist for management. In the acute phase (within 24 h), a variety of treatments have been proposed, such as ocular massage (to dislodge the embolus) and intravenous acetazolamide injection (to lower intraocular pressure) (125). However, there is no evidence from randomized trials regarding the efficacy of these treatments (126). It is important for physicians to measure the erythrocyte sedimentation rate to exclude giant cell arteritis (127). Regardless of treatment, however, the vision prognosis of central RAO is poor (128).

4. Corneal diseases

Patients with diabetes are known to exhibit abnormalities of the corneal epithelium, leading to corneal erosion, persistent epithelial defect, or corneal ulcers. Recurrent corneal erosions in patients with diabetes are usually posttraumatic and the result of apparently mild epithelial breakdown following cataract or vitreoretinal surgery (129–131). A reduction in hemidesmosomes may contribute to a weakness in the adhesion of diabetic corneal epithelium to the underlying stroma (132). In addition, erythrocyte aldose reductase increase has been reported in patients with type 2 diabetes, leading to high accumulation of sorbitol, which can damage the corneal epithelium (133). In one study, corneal abnormalities (gerontoxon, limbal vascularization, punctate keratopathy, endothelial dystrophy, recurrent erosion, and ulcers) were detected in up to 73.6% patients with diabetes (134). Patients with corneal disease often present with pain, photophobia, blurred vision, and hyperemia. However, patients with diabetes often have reduced corneal sensitivity as part of diabetes complication in peripheral nerves and limbal vasculopathy (135).

Patients with diabetes who wear contact lenses must take extra hygiene care and be warned to seek advice early if any irritation symptom develops to prevent vision loss from microbial keratitis. Treatment of corneal disease includes topical antibiotics and topical cycloplegic (short term), and corneal patching for 24 h is indicated if the original insult is of nonorganic nature (not from plant or soil sources), for large corneal lesions (>2 cm), and in non-contact lens users. Contact lens-related conditions including

corneal ulcers and large abrasions need urgent referral to the ophthalmologist. All other corneal cases need to be reviewed the next day by the primary care physician.

CONDITIONS MASQUERADING AS DIABETIC RETINOPATHY

There are a range of common ocular and systemic conditions that can mimic diabetic retinopathy in patients with diabetes (136).

1. Age-related macular degeneration

Although many population-based studies have shown that people with diabetes are not at higher risk of age-related macular degeneration (AMD) (137–143), there are similarities between AMD and diabetic retinopathy. First, retinal signs (e.g., hemorrhages and hard exudates) of neovascular or “wet” AMD are sometimes confused with diabetic macular edema, particularly among older patients with diabetes. Second, the key pathogenic process in neovascular AMD and proliferative retinopathy is an increased expression of VEGFs. Chronic inflammation is also a possible common pathophysiologic mechanism of both conditions (144,145). Advanced glycation end products, for example, have been found in drusen, a typical lesion of early-stage AMD (146). Third, there is now good evidence that anti-VEGF treatment is effective for both neovascular AMD and proliferative retinopathy (147–149).

2. Hypertensive retinopathy

Signs of hypertensive retinopathy are frequently seen in adults over 40 years of age and may include arteriosclerotic changes (arteriolar narrowing, arterio-venous crossing changes, or arterio-venous nicking), arteriolar wall changes (copper/silver wiring), cotton wool spots, hemorrhages, or edema. Many patients with diabetes have hypertension, and some of the more severe signs of hypertensive retinopathy are similar to diabetic retinopathy. Like diabetic retinopathy, the presence of hypertensive retinopathy signals widespread microvascular damage and predicts subsequent events of stroke, congestive heart failure, and cardiovascular mortality, independently of traditional risk factors (150–153). Early recognition of the ocular effects of blood pressure could allow physicians to better manage patients with hypertension and to monitor its end-organ effects (154).

3. Radiation retinopathy

Radiation retinopathy presents progressively degenerative and proliferative vascular changes, primarily affecting the macula, ranging from microaneurysm to telangiectasia, intraretinal hemorrhages, and neovascularization (155). Radiation retinopathy can have a delayed onset months to years after radiation treatment, and patients with diabetes and hypertension are more susceptible to radiation retinopathy (156) due to intensifying oxygen-derived free-radical assault on the vascular cells (155). Patients with minimal diabetic retinopathy undergoing chemotherapy may suffer vision loss from radiation retinopathy resulting from low-dose radiation that is considered to be safe and properly fractionated (157). Since radiation retinopathy and diabetic retinopathy are identical clinically and histopathologically, treatment for this condition has been based on established therapy for diabetic retinopathy such as laser photocoagulation (158).

4. Other causes of retinopathy

Typical diabetic retinopathy lesions such as cotton wool spots, retinal microaneurysms, and retinal hemorrhage are also seen in eyes with branch RVO. Other systemic conditions that may result in similar signs include HIV/AIDS (159), various connective tissue diseases (Bechet's disease, temporal arteritis, systemic lupus vasculitis, sarcoidosis, sickle cell retinopathy, and Wegener's granulomatosis), and retinal telangiectasias (Leber's miliary aneurysm, Coats' disease, and idiopathic juxtafoveal telangiectasia), a group of rare, idiopathic, congenital retinal vascular anomalies affecting the retinal capillaries.

CONCLUSIONS — A wide spectrum of ocular conditions other than diabetic retinopathy is associated with diabetes. Some of these conditions appear to be causally linked to hyperglycemia and diabetes (e.g., cataract), whereas diabetes may be only one of many risk factors for other conditions (e.g., RVO and retinal arteriolar emboli). In addition, there are a range of retinal conditions (e.g., hypertensive and radiation retinopathy) that mimic common diabetic retinopathy signs.

The management of diabetes-related eye diseases is primarily preventative, and regular eye examinations and appropriate ophthalmology referral remains the key strategy to reduce the impact of diabetes-

related vision loss. In many instances, vision loss associated with most of the conditions discussed is gradual. Occasionally, however, more urgent referral to an ophthalmologist is needed, as acute surgical or laser intervention can save a patient's vision. While clinical trials have demonstrated that good glycemic control reduces the incidence and progression of diabetic retinopathy (3), it is unclear whether the same beneficial effect applies to other diabetes-related ocular conditions (160). It is also unclear whether controlling for relevant risk factors (e.g., blood pressure and lipids) can alter the course of these ocular conditions.

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