Ocular Associations of Diabetes Other Than Diabetic Retinopathy

V. Swetha E. Jeganathan, mbbs[1,2]
Jie Jin Wang, phd[1,3]
Tien Yin Wong, md, phd[1,3,4]

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 ASSOCATED 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

From the [1]Centre for Eye Research Australia, University of Melbourne, Victoria, Australia; the [2]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore; the [3]Centre for Vision Research, University of Sydney, New South Wales, Australia; and the [4]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.
Corresponding author: Tien Yin Wong, twong@unimelb.edu.au.
Received 17 February 2008 and accepted 29 May 2008.
DOI: 10.2337/dc08-0342

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 opitc 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 ≥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 patients 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 autoregulation 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 vision 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 microvacular 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.

References

1. Congdon NG, Friedman DS, Lietman T: Important causes of visual impairment in the world today. *JAMA* 290:2057–2060, 2003
2. Kempen JH, et al: The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol* 122:552-563, 2004
3. Mohamed Q, Gillies MC, Wong TY: Management of diabetic retinopathy: a systematic review. *JAMA* 298:902–916, 2007
4. Cavallerano JD: A review of non-retinal ocular complications of diabetes mellitus. *J Am Optom Assoc* 61:533–543, 1990
5. American Optometric Association: Optometric Clinical Practice Guideline: Care of the Patient with Diabetes Mellitus [article online]. Available from http://www.aoa.org/documents/CPG-3.pdf. Accessed 25 January 2008
6. Stanga PE, Boyd SR, Hamilton AM: Ocular manifestations of diabetes mellitus. *Curr Opin Ophthalmol* 10:483–489, 1999
7. Rowe NG, et al: Diabetes, fasting blood glucose and age-related cataract: the Blue Mountains Eye Study. *Ophthalmic Epidemiol* 7:103–114, 2000
8. Hiller R, Sperduto RD, Ederer F: Epidemiologic associations with nuclear, cortical, and posterior subcapsular cataracts. *Am J Epidemiol* 124:916–925, 1986
9. Miglior S, et al: Risk factors for cortical, nuclear, posterior subcapsular and mixed cataract: a case-control study. *Ophthalmic Epidemiol* 1:93–105, 1994
10. Delcourt C, et al: Risk factors for cortical, nuclear, and posterior subcapsular cataracts: the POLA study: Pathologies Oculaires Liees a l'Age. *Am J Epidemiol* 151: 497–504, 2000
11. Klein BE, et al: Older-onset diabetes and lens opacities: the Beaver Dam Eye Study. *Ophthalmic Epidemiol* 2:49–55, 2005
12. Saxena S, Mitchell P, Rochtchina E: Five-year incidence of cataract in older persons with diabetes and pre-diabetes. *Ophthalmic Epidemiol* 11:271–277, 2004
13. McCarty CA, et al: Risk factors for age-related maculopathy: the Visual Impairment Project. *Arch Ophthalmol* 119:1455–1462, 2001
14. Mukesh BN, et al: Development of cataract and associated risk factors: the Visual Impairment Project. *Arch Ophthalmol* 124: 79–85, 2006
15. Leske MC, Chylack LT Jr, Wu SY: The Lens Opacities Case-Control Study: risk factors for cataract. *Arch Ophthalmol* 109:244–251, 1991
16. Hennis A, et al: Risk factors for incident cortical and posterior subcapsular lens opacities in the Barbados Eye Studies. *Arch Ophthalmol* 122:525–530, 2004
17. Foster PJ, et al: Risk factors for nuclear, cortical and posterior subcapsular cataracts in the Chinese population of Singapore: the Tanjong Pagar Survey. *Br J Ophthalmol* 87:1112–1120, 2003
18. Tsai SY, et al: Epidemiologic study of age-related cataracts among an elderly Chinese population in Shih-Pai, Taiwan. *Ophthalmology* 110:1089–1095, 2003
19. Nirmalan PK, et al: Risk factors for age related cataract in a rural population of southern India: the Aravind Comprehensive Eye Study. *Br J Ophthalmol* 88: 989–994, 2004
20. Leske MC, et al: Diabetes, hypertension, and central obesity as cataract risk factors in a black population: the Barbados Eye Study. *Ophthalmology* 106:35–41, 1999
21. Harding JJ, et al: Diabetes, glaucoma, sex, and cataract: analysis of combined data from two case control studies. *Br J Ophthalmol* 77:2–6, 1993
22. Bron AJ, et al: The lens in diabetes. *Eye* 7:260–275, 1993
23. Klein BE, Klein R, Lee KE: Diabetes, cardiovascular disease, selected cardiovascular disease risk factors, and the 5-year incidence of age-related cataract and progression of lens opacities: the Beaver Dam Eye Study. *Am J Ophthalmol* 126: 782–790, 1998
24. Kato S, et al: Glycemic control and lens transparency in patients with type 1 diabetes mellitus. *Am J Ophthalmol* 131:301-304, 2001
25. Klein BE, Klein R, Moss SE: Incidence of cataract surgery in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Am J Ophthalmol* 119:295–300, 1995
26. Negahban K, Chern K: Cataracts associated with systemic disorders and syndromes. *Curr Opin Ophthalmol* 13:419-422, 2002
27. Pirie A: Epidemiological and biochemical studies of cataract and diabetes. *Invest Ophthalmol* 4:629–637, 1965
28. Murtha T, Cavallerano J: The management of diabetic eye disease in the setting of cataract surgery. *Curr Opin Ophthalmol* 18:13–18, 2007
29. Hykin PG, et al: Extracapsular cataract extraction in proliferative diabetic retinopathy. *Ophthalmology* 100:394–399, 1993
30. Chew EY, et al: Results after lens extraction in patients with diabetic retinopathy: early treatment diabetic retinopathy study report number 25. *Arch Ophthalmol* 117:1600–1606, 1999
31. Cohen SM, et al: Endopthalmitis after pars plana vitrectomy: the Postvitrectomy Endopthalmitis Study. *Opthalmology* 102:705–712, 1995
32. Kattan HM, et al: Nosocomial endopthalmitis survey: current injcidence of infection after intreocular surgery. *Ophthalmology* 98:227–238, 1991
33. Montan PG, et al: Endopthalmitis after cataract surgery: risk factors relating to technique and events of the operation and patient history. *Ophthalmology* 105: 2171–2177, 1998
34. Scott IU, Flynn HWJ, Feuer W: Endopthalmitis after secondary intraocular lens implantation: a case-control study. *Ophthalmology* 102:1925–1931, 1995
35. Doft BH, et al. : Diabetes and postcataract extraction endopthalmitis. *Curr Opin Opthalmol* 13:147–151, 2002
36. Characteristics of patients with nonarteritic anterior ischemic optic neuropathy eligible for the Ischemic Optic Neuropathy Decompression Trial. *Arch Ophthalmol* 114:1366–1374, 1996
37. Flammer J, et al: The impact of ocular blood flow in glaucoma. *Prog Ret Eye Res* 21:359–393, 2002
38. Piltz-Seymour JR, et al: Optic nerve blood flow is diminished in eyes of primary open-angle glaucoma suspects. *Am J Ophthalmol* 132:63–69, 2001
39. Hayreh SS, et al: Nonarteritic anterior ischemic optic neuropathy: role of nocturnal arterial hypotension. *Arch Ophthalmol* 115:942–945, 1997
40. Arnold AC: Pathogenesis of nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol* 23:157–163, 2003
41. Hayreh SS, Podhajsky PA, Zimmerman B: Ipsilateral recurrence of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 132:734–742, 2001
42. Ischemic Optic Neuropathy Decompression Trial: twenty-four-month update. *Arch Ophthalmol* 118:793–798, 2000
43. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful: the Ischemic Optic Neuropathy Decompression Trial Research Group. *JAMA* 273:625–632, 1995
44. Yoles E, Wheeler LA, Schwartz M: Alpha2-adrenoreceptor agonists are neuroprotective in a rat model of optic nerve degeneration. *Invest Ophthalmol Vis Sci*

40:65–73, 1999
45. Kupersmith MJ, et al: Aspirin reduces the incidence of second eye NAION: a retrospective study. *J Neuroophthalmol* 17:250–253, 1997
46. Barr CC, Glaser JS, Blankenship G: Acute disc swelling in juvenile diabetes: clinical profile and natural history of 12 cases. *Arch Ophthalmol* 98:2185–2192, 1980
47. Bandello F, Menchini F: Diabetic papillopathy as a risk factor for progression of diabetic retinopathy. *Retina* 24:183–184, 2004
48. Sato T, et al: Development of bilateral, nonarteritic anterior ischemic optic neuropathy in an eye with diabetic papillopathy. *Jpn J Ophthalmol* 48:158–162, 2004
49. Hayreh SS, Zahoruk RM: Anterior ischemic optic neuropathy. VI. In juvenile diabetics. *Ophthalmologica* 182:13–28, 1981
50. Friedrich Y, et al: Diabetic papillopathy with macular star mimicking clinically significant diabetic macular edema. *Retina* 21:80–82, 2001
51. Pavan PR, et al: Optic disc edema in juvenile-onset diabetes. *Arch Ophthalmol* 98:2193–5219, 1980
52. Al-Haddad CE, Jurdi FA, Bashshur ZF : Intravitreal triamcinolone acetonide for the management of diabetic papillopathy. *Am J Ophthalmol* 137:1151–1153, 2004
53. Eshbaugh CG, et al : Simultaneous, multiple cranial neuropathies in diabetes mellitus. *J Neuroophthalmol* 15:219–224, 1995
54. Singh NP, et al: Multiple cranial nerve palsies associated with type 2 diabetes mellitus. *Singapore Med J* 47:712–715, 2006
55. Rush JA: Extraocular muscle palsies in diabetes mellitus. *Int Ophthalmol Clin* 24: 155–159, 1984
56. Watanabe K, et al: Characteristics of cranial nerve palsies in diabetic patients. *Diabetes Res Clin Pract* 10:19–27, 1990
57. Patel SV, et al: Diabetes and hypertension in isolated sixth nerve palsy: a population-based study. *Ophthalmology* 112: 760–763, 2005
58. Burde RM: Neuro-ophthalmic associations and complications of diabetes mellitus. *Am J Ophthalmol* 114:498–501, 1992
59. Kahn HA, Milton RC: Revised Framingham Eye Study prevalence of glaucoma and diabetic retinopathy. *Am J Epidemiol* 111:769–776, 1980
60. Dielemans I, et al: Primary open-angle glaucoma, intraocular pressure, and diabetes mellitus in the general elderly population: the Rotterdam Study. *Ophthalmology* 103:1271–1275, 1996
61. Mitchell P, et al: Open-angle glaucoma and diabetes: the Blue Mountains eye study, Australia. *Ophthalmology* 104:712–718, 1997
62. Hennis A, et al: Hypertension, diabetes, and longitudinal changes in intraocular pressure. *Ophthalmology* 110:908–914, 2003
63. Lin HY, et al: Intraocular pressure measured with a noncontact tonometer in an elderly Chinese population: the Shihpai Eye Study. *Arch Ophthalmol* 123:381-638, 2005
64. Bernth-Petersen P, Bach E: Epidemiologic aspects of cataract surgery. III. Frequencies of diabetes and glaucoma in a cataract population. *Acta Ophthalmol (Copenh)* 61:406–416, 1983
65. Katz J, Sommer A: Risk factors for primary open angle glaucoma. *Am J Prev Med* 4:110–114, 1988
66. Reynolds DC: Relative risk factors in chronic open-angle glaucoma: an epidemiological study. *Am J Optom Physiol Opt* 54:116–120, 1977
67. Morgan RW, Drance SM: Chronic open-angle glaucoma and ocular hypertension: an epidemiological study. *Br J Ophthalmol* 59:211–215, 1975
68. Wilson MR, et al: A case-control study of risk factors in open angle glaucoma. *Arch Ophthalmol* 105:1066–1071, 1987
69. Tielsch JM, et al: Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. *Ophthalmology* 102:48–53, 1995
70. Vijaya L, et al: Prevalence of open-angle glaucoma in a rural south Indian population. *Invest Ophthalmol Vis Sci* 46:4461-1167, 2005
71. Kahn HA, Milton RC: Alternative definitions of open-angle glaucoma: effect on prevalence and associations in the Framingham eye study. *Arch Ophthalmol* 98:2172–2177, 1980
72. Bengtsson B: The prevalence of glaucoma. *Br J Ophthalmol* 65:46–49, 1981
73. Armaly MF, et al: Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Arch Ophthalmol* 98:2163–2171, 1980
74. Grunwald JE, et al: Retinal autoregulation in open-angle glaucoma. *Ophthalmology* 91:1690–1694, 1984
75. Nakamura M, Kanamori A, Negi A: Diabetes mellitus as a risk factor for glaucomatous optic neuropathy. *Ophthalmologica* 219:1–10, 2005
76. Jacobson DR, Murphy RP, Rosenthal AR: The treatment of angle neovascularization with panretinal photocoagulation. *Ophthalmology* 86:1270–1277, 1979
77. Zeiter JH, Shin DH, Baek NH: Visual field defects in diabetic patients with primary open-angle glaucoma. *Am J Ophthalmol* 111:581–584, 1991
78. Mapstone R, Clark CV: Prevalence of diabetes in glaucoma. *Br Med J (Clin Res Ed)* 291:93–95, 1985
79. Mapstone R, Clark CV: The prevalence of autonomic neuropathy in glaucoma. *Trans Ophthalmol Soc UK* 104:265–109, 1985
80. Clark CV: Autonomic denervation hypersensitivity in the primary glaucomas. *Eye* 3:349–354, 1989
81. Schertzer RM, Wang D, Bartholomew LR: Diabetes mellitus and glaucoma. *Int Ophthalmol Clin* 38:69–87, 1998
82. Madsen PH: Experiences in surgical treatment of haemorrhagic glaucoma: a follow-up study. *Acta Ophthalmol Suppl* 120:88–91, 1973
83. Brown GC, et al : Neovascular glaucoma: etiologic considerations. Ophthalmology 91:315–320, 1984
84. Loffler KU: [Neovascular glaucoma: aetiology, pathogenesis and treatment]. *Ophthalmologe* 103:1057–1063, 2006 [Article in German]
85. Hohl RD, Barnett DM: Diabetic hemorrhagic glaucoma. *Diabetes* 19:944–947, 1970
86. Zirm M: Protein glaucoma–overtaxing of flow mechanisms? Preliminary report. *Ophthalmologica* 184:155–161, 1982
87. Sivak-Callcott JA, et al: Evidence-based recommendations for the diagnosis and treatment of neovascular glaucoma. *Ophthalmology* 108:1767–1776, 2001
88. Chen CS, Miller NR: Ocular ischemic syndrome: review of clinical presentations, etiology, investigation, and management. *Compr Ophthalmol Update* 8:17–28, 2007
89. Mizener JB, Podhajsky P, Hayreh SS: Ocular ischemic syndrome. Ophthalmology 104:859–864, 1997
90. Ino-ue M, et al: Ocular ischemic syndrome in diabetic patients. *Jpn J Ophthalmol* 43:31–35, 1999
91. Sivalingam A, et al: The ocular ischemic syndrome. II. Mortality and systemic morbidity. *Int Ophthalmol* 13:187–191, 1989
92. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis: North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 325: 445–453, 1991
93. Kawaguchi S, et al: Effect of carotid endarterectomy on chronic ocular ischemic syndrome due to internal carotid artery stenosis. *Neurosurgery* 48: 328–332, 2001
94. Kawaguchi S, et al: Effect of carotid artery stenting on ocular circulation and chronic ocular ischemic syndrome. *Cerebrovasc Dis* 22:402–408, 2006
95. Green WR, et al: Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Retina* 1:27–55, 1981
96. Christoffersen NL, Larsen M: Pathophysiology and hemodynamics of

branch retinal vein occlusion. *Ophthalmology* 106:2054–2062, 1999
97. Mohamed Q, et al: Interventions for central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology* 114:507–519, 2007
98. Shahsuvaryan ML, Melkonyan AK: Central retinal vein occlusion risk profile: a case-control study. *Eur J Ophthalmol* 13: 445–452, 2003
99. Sperduto RD, et al: Risk factors for hemiretinal vein occlusion: comparison with risk factors for central and branch retinal vein occlusion: the eye disease case-control study. *Ophthalmology* 105: 765–771, 1998
100. Rath EZ, et al: Risk factors for retinal vein occlusions: a case-control study. *Ophthalmology* 99:509–514, 1992
101. Mitchell P, W. Smith, Chang A: Prevalence and associations of retinal vein occlusion in Australia: the Blue Mountains Eye Study. *Arch Ophthalmol* 114:1243–1247, 1996
102. Hayreh SS, et al: Systemic diseases associated with various types of retinal vein occlusion. *Am J Ophthalmol* 131:61–77, 2001
103. Klein R, et al: The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 98: 133–141, 2000
104. The Eye Disease Case-Control Study Group: Risk factors for central retinal vein occlusion. *Arch Ophthalmol* 114: 545–554, 1996
105. Wong TY, et al: Cardiovascular risk factors for retinal vein occlusion and arteriolar emboli: the Atherosclerosis Risk in Communities and Cardiovascular Health studies. *Ophthalmology* 112:540–547, 2005
106. Pinna A, et al: Glucose-6-phosphate dehydrogenase deficiency in retinal vein occlusion. *Invest Ophthalmol Vis Sci* 48: 2747–2752, 2007
107. Natural history and clinical management of central retinal vein occlusion: the Central Vein Occlusion Study Group. *Arch Ophthalmol* 115:486–491, 1997
108. West JA, et al: Panretinal photocoagulation during cataract extraction in eyes with active proliferative diabetic eye disease. *Eye* 13:170–173, 1999
109. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion: the Central Vein Occlusion Study Group M report. *Ophthalmology* 102:1425–1433, 1995
110. Hirano Y, et al: Comparative study on efficacy of a combination therapy of triamcinolone acetonide administration with and without vitrectomy for macular edema associated with branch retinal vein occlusion. *Ophthalmic Res* 39:207–212, 2007
111. Margolis R, Singh RP, Kaiser PK: Branch retinal vein occlusion: clinical findings, natural history, and management. *Compr Ophthalmol Update* 7:265–276, 2006
112. Manuchehri K, Kirkby G: Vitreous haemorrhage in elderly patients: management and prevention. *Drugs Aging* 20:655–661, 2003
113. Hawkins WR: Venous occlusive disease review (Letter). *Retina* 27:514, 2007
114. Funderburk RL, Feinberg EB: Diabetes as a risk factor for retinal neovascularization in retinal vein occlusion. *Ann Ophthalmol* 21:65–66, 1989
115. Cugati S, et al: Retinal vein occlusion and vascular mortality: pooled data analysis of 2 population-based cohorts. *Ophthalmology* 114:520–524, 2007
116. Hayreh SS, Zimmerman MB, Podhajsky P: Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. *Am J Ophthalmol* 117:429–441, 1994
117. Lord RS: Transient monocular blindness. *Aust N Z J Ophthalmol* 18:299–305, 1990
118. Klein R, et al: Retinal emboli and stroke: the Beaver Dam Eye Study. *Arch Ophthalmol* 117:1063–1068, 1999
119. Bruno A, et al: Vascular outcome in men with asymptomatic retinal cholesterol emboli: a cohort study. *Ann Intern Med* 122:249–253, 1995
120. Klein R, et alL Retinal emboli and cardiovascular disease: the Beaver Dam Eye Study. *Arch Ophthalmol* 121:1446-14451, 2003
121. Wang JJ, et al: Retinal arteriolar emboli and long-term mortality: pooled data analysis from two older populations. *Stroke* 37:1833–1836, 2006
122. Breen LA: Atherosclerotic carotid disease and the eye. *Neurol Clin* 9:131–145, 1991
123. Recchia FM, Brown GC: Systemic disorders associated with retinal vascular occlusion. *Curr Opin Ophthalmol* 11: 462–467, 2000
124. Hondeghem K, Blanckaert M, Blanckaert J: Branch retinal artery occlusion in systemic diseases: a case report. *Bull Soc Belge Ophtalmol* 271:9–15, 1999
125. Klein BE, Klein R, Moss SE: Intraocular pressure in diabetic persons. *Ophthalmology* 91:1356–13560, 1984
126. Beatty S, Au Eong KG: Acute occlusion of the retinal arteries: current concepts and recent advances in diagnosis and management. *J Accid Emerg Med* 17:324–329, 2000
127. Hayreh SS, Zimmerman B, Kardon RH: Visual improvement with corticosteroid therapy in giant cell arteritis: report of a large study and review of literature. *Acta Ophthalmol Scand* 80:355–367, 2002
128. Yuzurihara D, Iijima H: Visual outcome in central retinal and branch retinal artery occlusion. *Jpn J Ophthalmol* 48:490–492, 2004
129. Fujishima H, Tsubota K: Improvement of corneal fluorescein staining in post cataract surgery of diabetic patients by an oral aldose reductase inhibitor, ONO-2235. *Br J Ophthalmol* 86:860–863, 2002
130. Hiraoka M, et al: Factors contributing to corneal complications after vitrectomy in diabetic patients. *Jpn J Ophthalmol* 45: 492–495, 2001
131. Brightbill FS, Myers FL, Bresnick GH: Postvitrectomy keratopathy. *Am J Ophthalmol* 85:651–655, 1978
132. Tabatabay CA, et al: Reduced number of hemidesmosomes in the corneal epithelium of diabetics with proliferative vitreoretinopathy. *Graefes Arch Clin Exp Ophthalmol* 226:389–392, 1988
133. Friedman EA: Advanced glycosylated end products and hyperglycemia in the pathogenesis of diabetic complications. *Diabetes Care* 22 (Suppl. 2):B65–B71, 1999
134. Didenko TN, et al: [Clinical and pathogenetic features of neurotrophic corneal disorders in diabetes]. *Vestn Oftalmol* 115:7–11, 1999 [Article in Russian]
135. Tavakoli M, et al: Corneal sensitivity is reduced and relates to the severity of neuropathy in patients with diabetes. *Diabetes Care* 30:1895–1897, 2007
136. Venkatramani J, Mitchell P: Ocular and systemic causes of retinopathy in patients without diabetes mellitus. *BMJ* 328:625–629, 2004
137. Vidaurri JS, et al: Association between drusen and some of the risk factors for coronary artery disease. *Ophthalmologica* 188:243–247, 1984
138. Algvere P, et al: Retinal microangiopathy and pigment epithelial lesions in subjects with normal, borderline, and decreased oral glucose tolerance. *Br J Ophthalmol* 69:416–419, 1985
139. Kahn HA, et al: The Framingham Eye Study. I. Outline and major prevalence findings. *Am J Epidemiol* 106:17–32, 1977
140. Hyman LG, et al: Senile macular degeneration: a case-control study. *Am J Epidemiol* 118:213–227, 1983
141. Blumenkranz MS, et al: Risk factors in age-related maculopathy complicated by choroidal neovascularization. *Ophthalmology* 93:552–558, 1986
142. Maltzman BA, Mulvihill MN, Greenbaum A: Senile macular degeneration and risk factors: a case-control study. *Ann Ophthalmol* 11:1197–1201, 1979
143. Voutilainen-Kaunisto RM, et al: Age-related macular degeneration in newly diagnosed type 2 diabetic patients and control subjects: a 10-year follow-up on evolution, risk factors, and prognostic significance. *Diabetes Care* 23:1672–1678, 2000
144. Hageman GS, et al: An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Re-*

tin Eye Res 20:705–732, 2001
145. Seddon JM, et al: Association between C-reactive protein and age-related macular degeneration. *JAMA* 291:704–710, 2004
146. Hammer M, et al: Ocular fundus autofluorescence observations at different wavelengths in patients with age-related macular degeneration and diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 246:105–114, 2008
147. Wong TY, G. Liew, Mitchell P: Clinical update: new treatments for age-related macular degeneration. *Lancet* 370:204–206, 2007
148. Rosenfeld PJ, et al: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 355:1419–1431, 2006
149. Gragoudas ES, et al: Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 351:2805–2816, 2004
150. Wong TY, et al: Retinopathy and risk of congestive heart failure. *JAMA* 293:63–69, 2005
151. Wong TY, Mitchell P: Hypertensive retinopathy signs are independent predictors of cardiovascular diseases (Letter). *Br Med J* 331:73, 2005
152. Wong TY, et al: Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet* 358:1134–1140, 2001
153. Wong TY, et al: Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA* 287:1153–1159, 2002
154. Wong TY, Mitchell P: Hypertensive retinopathy. *N Engl J Med* 351:2310–2317, 2004
155. Archer DB, Gardiner TA: Ionizing radiation and the retina. *Curr Opin Ophthalmol* 5:59–65, 1994
156. Gupta A, et al: Radiation retinopathy: case report and review (Letter). *BMC Ophthalmol* 7:6, 2007
157. Viebahn M, Barricks ME, Osterloh MD: Synergism between diabetic and radiation retinopathy: case report and review. *Br J Ophthalmol* 75:629–632, 1991
158. Graham CE, et al: Laser photocoagulation: ocular research and therapy in diabetic retinopathy. *Adv Exp Med Biol* 572: 195–200, 2006
159. Kramer M, Lynn W, Lightman S: HIV/AIDS and the eye. *Hosp Med* 64:421–424, 2003
160. Hoerle S, Kroll P: Evidence-based therapy of diabetic retinopathy. *Ophthalmologica* 221:132–141, 2007