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Comprehensive Review of the Effects of Diabetes on Ocular Health

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Keywords

Diabetes; macular edema; dry eye; cataracts; retinopathy; vasculopathy; neuropathy

Introduction

Diabetes afflicts 23.6 million people in the United States with an additional nearly 57 million individuals exhibiting prediabetic symptoms. By current estimates, the disease costs the healthcare system \$116 billion annually [1]. Type 1 diabetes, which has an autoimmune etiology accounts for approximately 10% of cases and largely affects children and young adults. In contrast, Type 2 diabetes accounts for 90% of cases and is associated with obesity and insulin resistance. It is estimated that up to 20% of patients diagnosed with type 2 disease actually have type 1.5, or latent autoimmune diabetes; these patients tend not to be obese nor do they exhibit insulin resistance.

Diabetes has the distinction of being the leading cause of blindness in adults. Diabetic retinopathy is a well known risk factor for visual impairment in diabetic patients [2], resulting in 12,000 to 24,000 new cases of blindness every year [301]. What is, perhaps, less appreciated is the fact that uncontrolled diabetes can adversely impact all ocular tissues. Thus, it is important that eye care professionals pay close attention to ocular changes in their diabetic patients so that all abnormalities can be treated early and monitored effectively. This article reviews the wide spectrum of diabetic complications in each of the ocular tissues.

Lids/Lashes

It has been reported that xanthlasma is more common in diabetic patients [3]. These sharply demarcated yellowish collections of cholesterol are not harmful or painful and can be easily removed from under the skin on or around the lids. Being generally more susceptible to infection, diabetics are more at risk of developing blepharitis [4] and orbital cellulitis [5]. It has been suggested that recurrent hordeola and blepharitis may be an early sign of diabetes in naive patients [6]. *Staphylococcus epidermis* was reported to be isolated from the lid margins of nearly all diabetics who were examined [7].

Conjunctiva

Diabetics are at increased risk of developing conjunctival bacterial infections [8–9] including acute infectious conjunctivitis [10]. Pathological changes in the conjunctiva were noted in up to 86% of diabetic patients [11]. These changes included a significant increase in squamous metaplasia and a reduction in goblet cell density [12–13]. Though not of clinical significance, several morphological changes in the conjunctival blood vessels have been reported in diabetic patients, which increased in expression with disease duration [14–15]. Microaneurysms in the bulbar conjunctiva were also reported to be more common in diabetics, with their incidence approaching 64% [16].

Dry Eye

Tear film abnormalities are common in diabetic patients, who also experience an increased incidence of dry eye. Tear break up time, an indicator of tear film stability, was reported to be diminished in diabetics [11–13,17]. In one study, tear break up time in nearly all diabetics tested was found to be less than 10 seconds, a finding only seen in 5.8% of controls [11]. Lower tear break up times in diabetics were reported to be associated with peripheral neuropathy and poorly controlled disease [12].

As mentioned above, studies have found a reduction in goblet cell density in the conjunctiva of diabetics [12–13], which may account, at least in part, for the reduced tear break up time seen in these individuals. Goblet cells produce the mucin layer of the tear film, which facilitates tear spreading and stability. One study reported a lack of mucin pickup on impression cytology in poorly controlled diabetic patients who also had peripheral neuropathy [12]. Diabetic patients were reported to exhibit diminished wetting in the Schirmer test, used to assess tear function [12,18]. Furthermore, a more severe reduction in total tear secretion was found in patients with nonproliferative retinopathy compared to those without retinopathy [13]. In concert with the above findings, patients whose dry eye symptoms worsened tended to be those whose serum glucose was poorly controlled [17,19]. An increase in dry eye was also reported in patients following panretinal photocoagulation, suggesting that damage to long ciliary nerves may occur during the procedure [12,17,20].

It is well known that diabetic patients exhibit reduced corneal sensitivity, which is thought to have a negative effect on reflex tear secretion [13,21]. Saito et al., reported that even a small reduction in corneal sensation was enough to significantly reduce reflex tearing [21]. Reduced corneal sensitivity also ironically leads to a reduction in the use of artificial tears [22].

In addition to the above-mentioned abnormalities in the diabetic tear film, it is thought that longstanding disease may cause damage to the microvascular supply to the lacrimal gland, impairing lacrimation [19]. A higher expression of advanced glycation endproducts (AGEs) and their receptors, as well as the transcription factor nuclear factor kappa-B (NF- κ B) was reported in the lacrimal glands of diabetic rats, suggesting that these factors may be involved in inducing the inflammatory alterations that are associated with dry eye in diabetes [23]. Finally, the presence of an abnormal tear film not only contributes to patient discomfort but also to the generation of ocular surface epithelial defects commonly found in diabetic patients [24].

Cornea

Keratopathy is a well described ocular complication of diabetes. Specifically, patients are at higher risk of developing several corneal complications including superficial punctate keratitis, recurrent corneal erosions, persistent epithelial defects and corneal endothelial damage [5,15,25]. Furthermore, the keratopathy that diabetics exhibit tends to be more severe [13]. These corneal complications have been linked to tear secretion abnormalities, decreased corneal sensitivity and poor adhesion between epithelial cells and their basement membrane [5,26–29].

Schultz et al., found corneal epithelial lesions ranging from superficial punctate keratitis to full thickness breaks in up to two thirds of their patients [7]. This same group also reported a correlation between the severity of keratopathy and the patients' diminished peripheral sensation, suggesting that their epithelial defects were yet another manifestation of generalized polyneuropathy [30–31]. In fact, reduced corneal sensitivity in diabetics is believed to be a symptom of the generalized polyneuropathy that occurs in these patients

[7,12–13,18,21,24,32–33]. In keeping with the notion that reduced corneal sensitivity is related to the severity of their diabetes, patients with this symptom were reported to exhibit more severe retinopathy and to have a longer disease duration [21,32].

While reduced corneal sensitivity contributes to dry eye, as described above, it also predisposes patients to corneal trauma, puts them more at risk of developing neurotrophic corneal ulcers [34], and adversely affects corneal wound healing [35–38]. Interestingly, high glucose was shown to independently suppress the epidermal growth factor receptor/phosphatidylinositol 3-kinase/Akt signaling pathway and attenuate corneal epithelial wound healing in cultured human corneal epithelial cells [39]. Corneal abrasions in diabetic patients have been reported to result in deeper damage than in individuals without diabetes, with some even leading to detachment of the basement membrane [40] and others resulting in recurrent corneal erosions.

Abrasions and recurrent epithelial defects have also been associated with intraocular surgeries in diabetics. In one study, nearly all of the 14 vitrectomy patients who exhibited corneal complications were diabetic [41]. This finding was supported by one study in which 83% of subjects who developed corneal complications following pars plana vitrectomies were diabetic [42] and another in which all of subjects with corneal complications were diabetics [43]. Of the patients with corneal complications, one study showed 9 of 13 with prolonged or recurrent epithelial defects [41] while another reported that about a quarter exhibited prolonged or recurrent epithelial problems following surgery [44].

The delay in reepithelialization seen in diabetic patients is thought to be due to the presence of abnormal adhesions of the epithelium to the underlying basement membrane. In support of this, an accumulation of AGEs was reported in the epithelial basement membranes of diabetic corneas [45]. Ljubimov et al., also found abnormal corneal basement membranes in diabetic patients, which were more prevalent in patients with retinopathy [46]. While abnormalities in the corneal basement membrane may explain the development of prolonged and recurrent epithelial defects, they have also been implicated in the reduced ability of the corneas to act as a barrier to infection. Studies by Gekka et al., and Gobbels et al., showed that corneal epithelial barrier function is weakened in diabetic patients, which correlated with higher HbA1c levels, longer duration of disease, and the presence of diabetic retinopathy [47–48]. Such a weakened barrier likely accounts for the fact that diabetic patients were reported to be more prone to the development of corneal infections such as fungal keratitis [49–51].

An increase in diabetic corneal thickness has been documented in several studies [52–55], with some suggesting that this may be one of the earliest changes detectable in the diabetic eye [52]. Increased central corneal thickness in diabetics was reported to be associated with increased HbA1c and blood glucose levels, and severe retinal complications [52–53]. While one study reported that increased corneal thickness correlated with a duration of disease of greater than 10 years [55], this was not confirmed in another [52]. It has been suggested that hyperglycemia causes corneal endothelial dysfunction that leads to increased corneal thickness. In support to this theory, Saini and Mittal found that type 2 diabetics had significantly more compromised corneal endothelial function than controls, and that endothelial function was most adversely affected in patients with diabetic retinopathy [54].

Wrinkles in Descemet's membrane were found in diabetic patients, most commonly in females [52,56–57]. While similar findings were reported in non-diabetic individuals with increasing age, they appear earlier in diabetics [57].

LASIK

Given the increased incidence of corneal defects in diabetic patients, there has been some concern as to whether or not laser in situ keratomileusis (LASIK) can be safely performed in these patients. The first report on this subject described poor refractive outcomes and epithelial complications in 47% of diabetic patients [58]. The authors believed that the keratopathy that these patients exhibited preoperatively accounted for their increased rate of corneal complications. Other studies reported an increased incidence of epithelial ingrowth in diabetic patients undergoing LASIK [59–62]. Cobo-Soriano et al., examined the outcomes of LASIKs performed on patients with underlying systemic conditions and reported no significant difference in refractive outcomes between diabetic patients and controls; only five diabetic patients out of 44 developed epithelial complications, all of which fully resolved without complication [63]. A case report by Ghanbari and Ahmadi described a patient with proliferative diabetic retinopathy who underwent LASIK. Within a month of surgery, the patient's retinopathy progressed dramatically, exhibiting extensive neovascularization of the iris and 360° neovascularization at the angle, which the authors attributed to the increased ischemic conditions during the suction phase of surgery. This case suggests that a history of proliferative diabetic retinopathy should be a contraindication for LASIK [64].

More recently, Halkiadakis and associates examined the outcome of LASIK in 24 tightly controlled diabetic patients. None of these patients displayed any significant epithelial complications and all ended up with a postoperative visual acuity (VA) of 20/20. The foregoing notwithstanding, 28% of these individuals ultimately required enhancements compared to 10% of non-diabetic patients [65]. These data suggest that LASIK is a relatively safe alternative for diabetic patients who are well controlled.

Contact Lenses

In light of the many deleterious effects diabetes can have on the cornea, it follows that these patients may be particularly susceptible to the development of contact lens related complications. Several studies have shown that diabetes increases the risk of contact lens-related microbial keratitis, especially in those who wear contact lenses on an extended schedule [66–67]. In addition, it was reported that of the four aphakic patients with hydrogel contact lenses who developed corneal ulcers [68], three were diabetic. It was reported that diabetic patients have higher levels of glucose in their tears than non-diabetics; while this may contribute to the development of ocular infections, it may similarly lead to increased lens spallation [56].

Several studies suggest that diabetics do not recover as readily from contact lens induced corneal edema as non-diabetics [69–71]; this is thought to be due to abnormalities in the corneal endothelium. A more recent study looked into the eye's response to hypoxia-induced corneal swelling and found that diabetic corneas showed significantly less edema than control patients. Other investigators reported similar findings and suggested that this reduced corneal swelling might be due to the effects of hyperglycemia on corneal hydration [70–72].

O'Donnell et al., looked at the ocular response of hydrogel contact lens wear in diabetic and control patients and found no significant difference between the two groups in ocular hyperemia, corneal staining, corneal sensitivity, corneal thickness, or VA [73]. Another study found no difference in contact lens complications, such as corneal staining and abrasions, between diabetic and control patients using daily wear soft contact lenses [74]. They concluded that current daily wear contact lenses are a safe option for vision correction in diabetic patients.

Iris

The most serious consequence of diabetes on the iris is neovascularization. This is most commonly observed around the pupil margin but if advanced, can involve the entire iris surface and angle [75]. This finding occurs in up to 7% of diabetic eyes and in up to 60% in eyes with proliferative retinopathy [76]. The cause is believed to be capillary dropout in the retina [77]. The fibrous tissue that accompanies neovascularization may contract causing ectropion uveae or peripheral anterior synechia [78].

The diabetic iris epithelium may become depigmented and has been reported to be three times more likely to release pigment [3]. The release of pigment from the iris accounts for the pigment deposits on the corneal endothelium and trabecular meshwork seen in these patients [79].

Pupil

Diabetic pupils tend to be more miotic [80]. Surgically-induced miosis following phacoemulsification was found to be much more pronounced in diabetic patients [81]. Diabetic patients may also have a weaker reaction to mydriatic drops [82], which is believed to be a manifestation of diabetic neuropathy resulting in reduced functional innervation of the dilator muscle [83]. The fact that patients exhibit a small pupil with intact light reflexes suggests that it is the sympathetic innervation of the iris that is most susceptible in diabetic eyes [84]. This was confirmed in histologic studies of the irides derived from diabetic cataract patients, which revealed a preferential loss of nerve terminals from the dilator muscle [85].

Uveitis

While some studies disputed a link between diabetes and uveitis [3,86–87], Rothova *et al.*, concluded that there was indeed such an association in light of the fact that 63% of their patients with idiopathic anterior uveitis were type 1 diabetics [88]. Long-term complications of uveitis were common in these patients, with half suffering from persistent posterior synechiae or cataracts. Most patients with diabetes and anterior uveitis were found to suffer from a severe systemic complication of diabetes such as angiopathy, nephropathy and/or neuropathy [88]. Guy *et al.*, reported a significant association between diabetic autonomic neuropathy and iritis. Accordingly, 30% of their type 1 diabetic patients who experienced neuropathy developed iritis compared to 0.7% of those without autonomic neuropathy. Interestingly, iritis developed before symptoms of autonomic neuropathy in all but two cases; the iritis in 11 of these patients was bilateral and recurrent [89].

Lens

Refraction

Though it is well accepted that diabetic patients experience transient changes in their refractive status, there have been conflicting reports regarding the type and cause of these changes. Duke-Elder [90] initially reported a shift towards myopia or hyperopia in association with hyperglycemia or hypoglycemia, respectively; these findings were confirmed by others [91]. More recent studies reported that the change in diabetic patients was more commonly towards hyperopia, especially upon initiation of treatment [92–95]. Regardless of the type of refractive change seen in patients, their prescription tends to normalize within weeks of treatment. There have been several mechanisms suggested for these transient changes, all of which implicate changes to the crystalline lens [93,95]. That said, Wiemer *et al.*, did report an effect of diabetes on the refractive power of the posterior

cornea; since this change did not affect total corneal power, it remains most likely that the refractive changes seen in diabetics is due to lens changes [96].

In addition to refractive changes, recent onset diabetics also exhibit changes in accommodation. Waite and Beetham reported transient paralysis of accommodation in 21% of diabetics, most commonly in patients between 20 and 50 years old [3]. Although some case reports described severe loss of accommodation in uncontrolled diabetics [91], a transient decrease which improves with proper control is more common [97]. A reduction in accommodative ability has also been described in patients who underwent panretinal argon laser photocoagulation [98].

Cataracts

Cataracts are a well known cause of visual impairment in diabetics. The Framingham Eye Study reported as much as a four-fold increase in the prevalence of cataracts in diabetics younger than 65 and up to a two-fold increase in patients over 65 [99–100]. Many studies, including the large population based Blue Mountains Eye Study [101] and Beaver Dam Eye Study [102], reported an increased prevalence and incidence of posterior subcapsular cataracts in diabetic patients [103–107]. There have also been reports of an increased incidence of cortical cataracts in diabetics, though this association has been less consistent [101–102, 104–105, 107–109]. Though the relationship between diabetes and nuclear cataracts is weaker [101, 106–109], it is interesting to note the Beaver Dam Eye Study found that a 1% increase in HbA1c increased the risk of nuclear cataracts by 15% in diabetic patients [102].

The Blue Mountains Eye Study also found a significant relationship between impaired fasting glucose, which is an indication of pre-diabetes, and the incidence of cortical cataracts. Specifically, the data showed that pre-diabetic patients had a two-fold higher risk of developing cortical cataracts than patients with normal fasting glucose [110]. Klein et al., reported that the duration of disease was the most important risk factor for the development of cataracts in patients with early-onset diabetes [99]; their findings were supported by others [111]. Negahban and Chern found that higher levels of hyperglycemia were associated with a higher risk of developing cataracts [111].

Snowflake cataracts, which are white subcapsular opacifications, have been described in young type 1 diabetics. This type of cataract is less commonly seen today because it is usually associated with long-term untreated hyperglycemia [112]. Posterior lens opacifications have been reported to clear in diabetic patients who achieve tight glycemic control [113–115].

Though a report suggested that there was no association between the type of diabetic treatment and cataract formation [99], others suggested that different treatments posed different risks. Both Prchal et al. and Panchapakesan et al. concluded that oral hypoglycemic medications were associated with posterior subcapsular cataracts [106, 117]. Data from Klein et al. suggested that older onset diabetics using insulin were at a higher risk of requiring cataract surgery than those treated by diet or medications [116].

Cataract Surgery

Cataract surgery is not only of obvious importance in improving vision in diabetic patients, but also because it allows for the clear assessment of retinal health. Cataracts tend to develop earlier and progress more rapidly in diabetic patients, often necessitating surgical intervention at an earlier age [99]. Aiello et al., reported an increased risk of neovascularization of the iris as well as neovascular glaucoma in diabetic patients who

underwent intracapsular cataract extraction, regardless of the patient's severity of preoperative retinopathy [118].

A link has been established between final visual outcome and the degree of diabetic retinopathy present at the time of surgical extracapsular cataract extraction (ECCE). In patients with no preoperative retinopathy, 87% had a VA of 20/40 or better postoperatively, while none of the patients with active preoperative proliferative retinopathy achieved an acuity better than 20/40 [119]. Kodama et al., reported that progression of retinopathy was more common in ECCE diabetic patients with elevated HbA1c levels and in those treated with insulin compared to patients who controlled their diabetes through diet or oral hypoglycemic medications [120]. Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) suggest that the most important predictor of decreased vision following cataract surgery is the severity of preoperative retinopathy [121]. Interestingly, in this study, patients with moderate to severe non-proliferative diabetic retinopathy at the time of cataract extraction achieved some vision improvement, with 55% achieving a two line improvement in VA [121]. The fact that 81% of ETDRS patients received some photocoagulation therapy prior to cataract surgery could have accounted for the better visual outcomes reported in this study [121]. This view is supported by the results of Suto et al., [122] that confirmed the importance of preoperative macular edema treatment in securing better final visual outcomes after cataract surgery.

Reports regarding the effects of cataract surgery on the acceleration of the progression of diabetic retinopathy have been conflicting. Some have reported evidence of progression following ECCE [120,123–125], with one study concluding that the retinopathy in nearly all patients increased following surgery [125]. It has been suggested that this increased risk may be moderated by the use of phacoemulsification for cataract extraction. Parenthetically, eyes that had phacoemulsification had a two-fold increased risk of developing retinopathy compared to eyes that were not subjected to cataract surgery [126]. Other groups, however, failed to find evidence of the progression of retinopathy in their surgical patients [127–129].

As with the progression of retinopathy, it has also been a concern that cataract surgery may cause a progression of diabetic macular edema. Several studies, including the ETDRS, did not find an association between clinically significant macular edema and cataract extraction [121,127–129]. Biró and Balla measured macular thickness using optical coherence tomography (OCT) in diabetic and non-diabetic eyes following phacoemulsification and found that there was no significant difference in macular edema between the two groups [130]. Similarly, Dowler et al., failed to uncover a significant difference between ECCE and phacoemulsification vis-à-vis the progression of their patients' macular edema or retinopathy [131].

Posterior capsular opacification (PCO) is a common finding following cataract surgery. A higher incidence of PCO was reported in diabetic patients following ECCE compared to controls; patients with severe retinopathy were more apt to develop PCO [131]. Conflicting results were reported by Zaczek and Zatterstrom, who found that the rate of PCO was significantly reduced in diabetic patients two years after phacoemulsification [132].

A report published within the last year [133] described several small scale studies that combined intravitreal bevacizumab or sub-Tenon's triamcinolone with cataract surgery to improve the visual outcome in diabetic patients at high risk of developing postoperative macular edema or retinopathic progression [134–138].

Aqueous Humor

The reported effects that diabetes has on aqueous humor dynamics have not been consistent. While two studies suggested that diabetics exhibit a reduced rate of aqueous formation [139–140], others found this hyposecretion to be mild and not clinically significant [141]. Aqueous vascular endothelial growth factor (VEGF) was reported to be positively associated with clinically meaningful changes in central subfield thickness in diabetic patients [142].

Endophthalmitis

Endophthalmitis is a serious complication of cataract surgery. Fahmy [143] and Montan et al., [144] did not find diabetes to be a risk factor for this condition, though several other groups did [145–147]. While postoperative endophthalmitis is rare following vitrectomy, one study reported that most of the patients that did develop this complication were diabetic [148].

Though this condition primarily develops as a result of surgery or trauma, there have been reports of endogenous endophthalmitis. In a study of patients with endophthalmitis caused by *Klebsiella pneumonia*, over 90% of cases involved newly diagnosed or poorly controlled diabetics [149]. Endogenous endophthalmitis caused by *Escherichia coli* was reported to be almost exclusively found in diabetic patients [150–151].

Vitreous

The vitreous in diabetic patients undergoes abnormal collagen crosslinking and non-enzymatic glycation [152], which lead to precocious liquefaction and posterior vitreous detachment (PVD) [153–154]. Diabetics have been shown to exhibit vitreous degeneration [153–155] in a manner similar to that normally seen in older adults [155].

It has been suggested that the vitreal synchysis and syneresis induced by the above changes play a role in proliferative diabetic retinopathy (PDR) [154–156]. New vessels growing on the retina project into the posterior vitreous and changes within the vitreous may exert traction on these vessels resulting in vitreal hemorrhaging and vision loss [157]. Interestingly, a lower incidence of PDR has been reported in patients who underwent complete PVD and an increased risk of aggressive proliferation in the eyes of patients who underwent partial PVD [158].

Asteroid hyalosis (AH) is a condition, typically unilateral, in which globules composed of fat and calcium form in the vitreous; the condition rarely affects visual functioning. While in the past, it was suggested that AH was more prevalent in diabetics [159–160], recent large scale studies have not uncovered a significant association between AH and diabetes [160–163]. More recent studies using galactose fed beagles found an increased incidence of asteroid hyalosis in animals with advanced stages of retinopathy [164], suggesting that AH develops as a result of the diffusion of lipid into the vitreous from the retina as the latter undergoes degeneration.

Mucormycosis

Mucormycosis is a rare but highly aggressive, and often fatal, fungal infection affecting immunocompromised individuals and type 1 diabetics in diabetic ketoacidosis (DKA) [165–167]. Infection usually begins in the palate or paranasal sinuses from where it readily spreads to the orbital contents. Clinical presentation may include proptosis, loss of vision, ocular pain, and ophthalmoplegia. The infection tends to invade arteries and lead to

infarction of tissues and thrombosis. Treatment includes aggressive use of Amphotericin B and surgical debridement [165–166,168].

Retinopathy

Risk Factors

Studies suggest that the most consistent risk factors for the development and severity of retinopathy are duration of diabetes, younger age at diagnosis, high glycosylated hemoglobin levels, and high systolic blood pressure [169–177]. Ocular perfusion pressure has also been associated with an increased incidence of retinopathy in younger-onset patients, suggesting the potential effectiveness of regulation of both elevated intraocular pressure (IOP) and blood pressure [178] in the treatment of retinopathy. The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported an inverse relationship between small body mass and the incidence and severity of retinopathy [171,179]. A higher prevalence of diabetic retinopathy has been reported in blacks, which may be due to the higher incidence of other risk factors associated with vision loss in these individuals, such as hypertension [180].

Cigarette smoking is a well known risk factor for the development of vascular disease. Smoking has been shown to increase risk of developing diabetes as well as diabetic retinopathy [181–183]. While smoking cessation can facilitate glycemic control and reduce the risk of diabetic complications, short-term risk may increase due to its oft-associated weight gain [184]. The effects of pregnancy on diabetic retinopathy are unclear and remain controversial but there is reason to believe that some women experience worsening of their retinopathy as a result of pregnancy [185–187]. Women with pre-existing retinopathy, especially proliferative changes, were reported to benefit from laser photocoagulation when given prior to pregnancy [185–186]. Duration of diabetes greater than 15 years, poor glycemic control, and hypertension appear to be major determinants for the development and progression of diabetic retinopathy during pregnancy [186].

Alcohol consumption, lifestyle, and socioeconomic status were also reported to be risk factors. Perhaps not unexpectedly, diabetic retinopathy has been shown to correlate with systemic circulatory disease including cardiovascular disease, nephropathy, and overall mortality [188–190].

It is now well known that the Diabetes Control and Complications Trial (DCCT) Research Group reported slowed progression of retinopathy, reduced development of proliferative or severe nonproliferative retinopathy, less macular edema and less need for panretinal photocoagulation in well controlled diabetics [191]. The United Kingdom Prospective Diabetes Study (UKPDS) reported similar reductions in overall microvascular complications in type 2 diabetics who were tightly controlled [192–193].

Clinical Features

Diabetic retinopathy consists of a spectrum of lesions, located primarily in the posterior pole of the retina within five to ten disc diameters of the optic nerve head. Retinopathy can be classified into 4 stages of nonproliferative diabetic retinopathy (including one in which disease is not apparent) and two stages of proliferative retinopathy, any of which can include the involvement of diabetic macular edema. With appropriate treatment, clinical trials have shown that severe vision loss can be prevented in most patients [194].

The hallmark of mild non-proliferative diabetic retinopathy (NPDR) is the presence of microaneurysms in the absence of other retinal abnormalities. The overall risk of developing vision loss is low in these patients, though a high rate of microaneurysm formation alone has

been shown to be a biomarker for the later development of clinically significant macular edema (CSME) [195]. Microaneurysms are also found in moderate NPDR, usually accompanied by any or all of the following: soft exudates (cotton wool spots), venous beading, and mild intra-retinal microvascular abnormalities (IRMA). Hard exudates may also be found at this stage and are important to note since they may signify areas of retinal edema or thickening. Patient with this stage of retinopathy have only a 3–9% risk of developing high risk PDR within a year. Close monitoring, rather than treatment, is indicated for this condition.

The simplified method for defining severe NPDR uses the 4:2:1 rule and only one finding needs to be present to qualify for this level. The retina must exhibit extensive retinal hemorrhages, greater than 20 in each of the 4 quadrants, 2 quadrants of definite venous beading, or prominent intraretinal microvascular abnormalities (IRMA) in at least one quadrant, and no signs of proliferative disease. Patients who fall into this category are considered high risk and half go on to develop some degree of PDR within a year. Treatment of this stage with panretinal photocoagulation has proven beneficial and should be considered, especially in those with type 2 diabetes [194,197].

Neovascularization of the disc or elsewhere is considered early PDR. These new vessels fan out of the plane of the optic nerve and retina and may be difficult to observe. They are fragile and often tear resulting in preretinal or vitreous hemorrhaging. In high-risk proliferative PDR, patients display moderate or severe neovascularization on or within 1DD of the disc (new vessels of the disc - NVD) which is greater than 1/4 to 1/3rd the disc area, mild NVD if fresh vitreous or preretinal hemorrhaging is present, or moderate or severe neovascularization elsewhere (NVE) if a fresh vitreous or preretinal hemorrhage is present. Such patients have a 25% risk of severe vision loss within 2 years if left untreated. Panretinal laser photocoagulation is the indicated treatment for high risk PDR and was shown to be effective in reducing severe vision loss by 50% [194,198]. If left untreated, neovascular proliferation penetrates the inner limiting membrane and spreads onto the retinal surface. These vessels can then enter the vitreous cavity and attach to the posterior vitreous face leading to contraction and distortion of the vitreous. This often results in rupturing of these fragile capillaries resulting in pre-retinal or vitreous hemorrhaging that can lead to sudden vision loss. The Diabetic Retinopathy Vitrectomy Study evaluated the benefits of early surgery for vitreous hemorrhages versus observation and found that only younger diabetics benefited from early surgery [199–200].

Treatment of retinopathy with VEGF inhibitors, such as pegaptanib (Macugen), bevacizumab (Avastin) and ranibizumab (Lucentis), has shown promise. Of these agents, Macugen is the most selective inhibitor, only targeting VEGF₁₆₅. This VEGF isoform is thought to play a key role in pathologic neovascularization and its use may be associated with fewer systemic side effects compared to other, less selective inhibitors [201,202]. Avastin was reported to be particularly effective in treating neovascularization of the iris (NVI) and neovascular glaucoma [203,204]. Additionally, when used in combination with pan retinal photocoagulation (PRP), Avastin increased the amount and rate of neovascular regression and decreased the incidence and severity of PRP-associated macular edema [205,206,207]. Lucentis was reported to be effective in the treatment of diabetic macular edema [208,209,210]; how it will fair in combination treatment with PDR remains to be determined.

Macular edema

A patient is said to have clinically significant macular edema if 1) retinal thickening is located at or within 500 microns (1/3 DD) from the center of the macula; or 2) hard exudates are found within 500 microns of center of the macula if associated with thickening of the

adjacent retina; or 3) zones of retinal thickening 1DD in size are present at least a part of which is within 1DD of the center of the macula. Diabetic macular edema (DME) is among the leading causes of persistent, severe vision loss in patients with diabetic retinopathy. The presence of hard retinal exudates, which often accompany the edema, was reported to be associated with high serum cholesterol/lipid levels [211–214]. Interestingly, retinal hard exudates alone have also been shown to be an independent risk factor for visual impairment [212]. Observational data suggest that by lowering serum lipid levels, patients with diabetic retinopathy may reduce their overall risk for vision loss.

In patients with CSME, fundus fluorescein angiography may be important in identifying the extent and type of leakage, thereby facilitating the formulation of a treatment strategy. Focal or grid laser treatment was proven by the ETDRS to be beneficial in patients with CSME and it has also been shown to reduce the progression of moderate visual loss by 50% [215]. Adding intravitreal triamcinolone as an adjunct to standard laser treatment for the control of CSME was not shown to be of long term benefit [216,217]. Optical coherence tomography (OCT) facilitates the detection of CSME, particularly sub-clinical edema, and also allows for the assessment of the effects of vitreous traction on macular changes [218].

Tractional Elevations of the Retina

Tractional retinal detachments and tractional retinoschisis are well known complications of PDR. Diabetic patients become susceptible to these retinal changes when capillary ischemia weakens intraretinal connections resulting in tractional lamellar separation. Tractional detachments can develop after retinal photocoagulation for the treatment of fibrovascular membranes [219]. Some studies suggest that the size of the tractional retinal detachment and extent of preretinal fibrosis are the highest risk factors associated with progression to retinal breaks or rhegmatogenous detachment [220]. Tractional rhegmatogenous detachments require immediate surgical repair due to their rapidly progressive nature and risk of foveal involvement. Pars plana vitrectomy improves anatomical and functional visual outcome in patients with tractional retinal detachments, especially when the macula is involved [221,222].

Retinal Vein and Artery Occlusion

Diabetes correlates highly with retinal vein occlusion [223–227]. Diabetic patients often exhibit increased red blood cell and platelet aggregation along with increased synthesis of fibrinogen and alpha-2-globulin [228]. Conditions that increase blood viscosity lead to an increase in turbulent flow and predispose the eye to development of central retinal vein occlusion (CRVO). Hypertension and other thrombophilic risk factors have also been shown to increase the risk of occlusions [229]. The hypercoagulable state of diabetic patients may also predispose them to artery occlusions.

Ocular Ischemic Syndrome

Apart from the many complications associated with diabetic microangiopathy, diabetes also increases the risk of macrovascular changes such as carotid occlusive disease resulting in significant ocular changes referred to as ocular ischemic syndrome (OIS). In addition to diabetes, the most common risk factors for OIS are hypertension, coronary artery disease, a prior stroke, and hemodialysis [230–232]. Chronic ocular hypoperfusion can lead to progressive retinal and anterior segment ischemic changes with profound visual consequences. The most common presenting signs of OIS are gradual or sudden vision loss, amaurosis fugax, iris and angle neovascularization, neovascular glaucoma, optic disc pallor and edema, disc and retinal neovascularization, venous stasis and retinal hemorrhages [230–232]. Recognition of the ischemic changes associated with OIS can be challenging because they tend to mimic and even mask diabetes-related changes in the eye. That said, diabetic

retinopathy is generally most concentrated within the retinal arcades in the posterior pole and appears fairly symmetrically between the two eyes whereas venous stasis retinopathy and anterior segment ischemia associated with OIS are typically unilateral, with retinal hemorrhages located outside of the arcades in the midperipheral fundus. The presence of unilateral retinopathy in a diabetic patient, especially if present with iris neovascularization, should always lead the clinician to suspect carotid occlusive disease. Proper detection and diagnosis of carotid occlusive disease is important, as visual prognosis tends to be poor, especially when iris neovascularization is present. Treatment with panretinal photocoagulation, trabeculectomy and carotid reconstruction has little or no effect on visual outcome [230,231].

Lipemia Retinalis

Lipemia retinalis, a relatively rare disorder that develops primarily in ketotic diabetics with severe hypertriglyceridemia [233,234], is characterized by creamy white-colored retinal blood vessels. The condition is not usually associated with long term visual changes if treatment for hyperlipidemia, and ketoacidosis if indicated, are administered appropriately. If blood lipid levels are extremely high, the aqueous humor itself may also take on that appearance [235].

Optic Neuropathy

Diabetic Papillopathy

Diabetic papillopathy (DP) is characterized by optic disc edema but an absence of optic nerve dysfunction, normal intracranial pressure, a lack of nerve inflammation, infiltration or infection [236–241], and no afferent pupillary defects (APD) or dyschromatopsia [241]. The condition is self limiting and vision generally recovers to better than 20/30 in most patients [240]. Occurrence is rare, with an incidence of 0.5% reported by Regillo et al., [241]. It is important for clinicians to be aware that this condition can mimic papilledema [242] and optic nerve neovascularization [243].

Anterior Ischemic Optic Neuropathy

Anterior ischemic optic neuropathy (AION) is clinically classified as an acute, pallid optic disc swelling (followed by optic nerve pallor) with APD associated with visual field defects [236]. Telangiectasia of disc vessels may occur, which may be mistaken for disc neovascularization [244]. AION is thought to be precipitated by circulatory insufficiency in nonarteritic ischemic optic neuropathy (NAION) [245]. Diabetic patients are at increased risk of developing NAION [246–248]. A study by the Ischemic Optic Neuropathy Decompression Trial Study Group, designed to determine the baseline clinical characteristics of patients with NAION, found that 24% of patients had a history of diabetes [246]. Patients with NAION in one eye were reported to have an increased incidence of optic disc crowding in their contralateral eye [249–253].

Optic nerve decompression surgery did not only fail to improve the visual outcome in these patients [254] but was associated with a worse prognosis [255]. Aspirin treatment appeared to reduce the occurrence of NAION in the contralateral eye of patients in a retrospective study [256]. While neuroprotective agents have been beneficial for the treatment of secondary neuronal degeneration in animal models, further studies will be needed in order to determine if they are effective in the treatment of NAION [257].

Glaucoma

Glaucoma affects an estimated 70 million people worldwide, of which 6.7 million are blind secondary to the disease process [258]. It is an optic neuropathy defined by changes in the

optic nerve and associated visual field defects. While patients may or may not present with elevated IOP, interestingly, significantly elevated IOP has more often been reported in diabetics than non-diabetics [259–263]. The Beijing Eye Study reported an association between ocular hypertension (OHT) and diabetes [262]. Interestingly, diabetes was reported to reduce the risk of advancement from OHT to open angle glaucoma (OAG)[264]. This was supported by the Singapore Malay Eye Study which found that while IOP was significantly higher in patients with diabetes, these patients did not go on to develop more OAG than non-diabetic subjects [260]; these results were supported by others [261,263]. Several studies did, however, report a direct association between OAG and diabetes. The Beaver Dam Eye Study [265], the Blue Mountains Eye Study [266], and the Nurses' Health Study [267] all found a significant association between diabetes and glaucoma. The Los Angeles Latino Eye Study reported that OAG was 40% more prevalent in type 2 diabetic Latino subjects, especially those with diseases of long duration [268].

A 2004 meta analysis concluded that diabetes increases the risk of primary OAG (POAG) by 1.5 fold [269]. An increased risk of progression of POAG was reported in diabetic patients in the Advanced Glaucoma Intervention Study (AGIS)[270] and Collaborative Initial Glaucoma Treatment Study (CIGTS) [271]. In contrast, the Barbados Incidence Study of Eye Diseases, the Melbourne Visual Impairment Project, and the Rotterdam Eye Study [272–275] failed to conclude that diabetes was a risk factor for the development of POAG. These findings were in agreement with those of the Singapore Malay Eye Study and the Baltimore Eye Study [260,261]. The Early Manifest Glaucoma Trial [276,277], the Collaborative Normal Tension Glaucoma Study [278], and a study by Kooner *et al.*, [279] found no associated increased risk of POAG progression and diabetes. An increased incidence of narrow angle glaucoma was reported in type 2 diabetics and individuals with impaired glucose tolerance [280]. One important contributing factor was speculated to be the effect of elevated serum glucose on lens swelling, which can directly lead to angle closure [6].

Neovascular glaucoma (NVG) is a complication of PDR that is thought to develop as a result of VEGF-induced neovascularization of the iris and angle [281].; the newly formed blood vessels and fibrous tissue block aqueous outflow from the anterior chamber. It is estimated that up to 43% of NVG is caused by PDR [282]. Current therapy involves immediate treatment to reduce IOP and subsequent pan-retinal photocoagulation, the latter of which was shown to induce vascular regression if applied early [283–284]. Visual prognosis in NVG is poor [285]. A recent study by Vasudev *et al.*, reported somewhat improved, but still poor, visual outcome in patients treated with Bevacizumab and PRP [286].

Wolfram Syndrome

Wolfram Syndrome is a rare condition characterized by type 1 diabetes and optic atrophy; progressive impairment of hearing has also been associated with this condition [287,288]. The estimated prevalence of Wolfram Syndrome is one in 770,000 in the general population and one in 150 cases of type 1 disease [287]. The key ophthalmologic finding in these patients is optic atrophy [288], though low VA, color vision defects, and visual field defects have also been described [289].

Cranial Nerve Palsies

Cranial nerve mononeuropathies are a well documented diabetic complication, specifically those affecting the third, fourth, sixth, and seventh cranial nerves [290–293]; multiple neuropathy has been less commonly reported [292,294,295]. Watanabe *et al.*, found a 1% incidence of cranial nerve palsy in diabetic subjects over a 25 year period [291], which

represented a 7.5 fold increase in incidence compared to non-diabetic subjects. Interestingly, diabetic patients with cranial nerve palsies were reported to have significantly less diabetic retinopathy [292]. Cranial nerve mononeuropathy classically presents with an abrupt onset and is characterized by transient pain, absence of other neurologic involvement, and spontaneous recovery in 3 to 6 months [296–298], though alpha-lipoic acid has been shown to significantly accelerate recovery [299].

The study by Watanabe et al., found that the most common mononeuropathies in diabetic patients were oculomotor and facial nerve palsies [291]. In contrast, a Mayo Clinic study reported that the most commonly acquired cranial nerve palsy independent of etiology involved the abducens nerve, followed sequentially by the oculomotor and trochlear nerves [296]. While the Mayo Clinic study did not specifically categorize the frequency of cranial nerve palsies in diabetic patients, a more recent study that did found that the abducens nerve was most frequently involved (50.0%), followed by the oculomotor (43.3%) and trochlear (6.7%) nerves [292].

The development of sixth nerve palsies in diabetics is often attributed to the patients' history of microvascular ischemia [296]. Similarly, third nerve mononeuropathy with pupil sparing is largely associated with diabetic microvascular disease. A prospective study by Jacobson found pathological anisocoria in 10 of 26 patients with diabetic oculomotor nerve palsy [300]; the degree of anisocoria was typically less than 1 mm and the pupil always remained reactive. In light of the fact that pupil involvement in third nerve palsy is typically seen in aneurysmal palsies, Trobe [301], in an editorial accompanying Jacobson's study, suggested that catheter angiography be performed in patients with acquired third nerve palsy who have an anisocoria greater than 2 mm.

Stroke-Induced Vision Loss

It is clear that diabetes is a significant risk factor for stroke [302–305]. Data suggest that a significant minority of diabetic patients who reported a history of stroke had visual field defects [302]. The prevalence of homonymous visual field defects in this study was associated with diabetes. Of concern is the fact that nearly half of these patients with homonymous field defects were still driving, highlighting the importance of routine screening for visual field defects in this population.

Conclusion

It is clear that patients with uncontrolled diabetes are at risk of developing a wide range of ocular pathology. While treatment of sight-threatening retinal disease is paramount in these patients, the information in this review clearly shows that visual morbidity can also result from diabetes-induced infection as well as damage to the optic nerve, cornea, uveal tract, orbital tissues and lids, cranial nerves that innervate the extraocular muscles, and lens.

Summary

- In light of the potential devastating effects of diabetes on ocular health, it behooves the eye care professional to pay close attention to ocular changes in their diabetic patients so that they can be treated early and effectively. In this review, anterior and posterior segment changes and disease are reviewed in depth, including extraocular, neurological, and optic nerve changes. The intention of this review is to provide a ready resource to clinicians regarding the full range of ocular complications associated with diabetes.

Expert Commentary

- Individuals with uncontrolled diabetes develop a variety of ocular pathologies that affect nearly all tissues in the eye. While the more well known complications are sight-threatening retinopathy, macular edema, and cataract, it is important to be aware of the effects of this disease on the other ocular tissues, the result of which can also be compromised visual function. Recent advancements in the treatment of some of these complications, such as the use of VEGF inhibitors and intravitreal steroid injections have improved the visual outcome in patients. However, other advances in eye care such as LASIK have presented diabetics with new challenges. The most important approach to the prevention of ocular complications in diabetic patients remains the maintenance of tight glycemic control.

5 Year View

- It is estimated that before too long, one in three Americans may develop diabetes if current trends continue. Such a frightening statistic has implications vis-à-vis the importance of research in the areas of diabetes pathogenesis, prevention, treatment, and management. We may be close to making important advances in preventing autoimmune diabetes through immune modulation. On the other hand, our best approach to preventing type 2 disease remains reducing obesity by educating the public regarding the salutary nature of good nutrition and exercise. Cutting edge research into the epigenetic factors that play a role in disease pathogenesis will also be important in developing new treatment approaches. Unfortunately, at least in the near-term, it is likely that the numerous ocular complications of diabetes will remain commonplace in clinical practice.

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WEBSITES

1. (70) CDC. National Diabetes Fact Sheet. 2007. <http://www.cdc.gov/diabetes/pubs/estimates07.htm>

FIGURE 1.

Left: Advanced visually significant posterior subcapsular cataract in the right eye at initial presentation. *Right:* Advanced visually significant posterior subcapsular cataract in the left eye at initial presentation. (Reproduced with permission from Sharma, P, Vasavada, AR. J Cataract Refract Surg 27:789–794, 2001)

Left: Progressing centripetal regression of the posterior subcapsular cataract in the right eye 3 weeks after the initial presentation. *Right:* Irregular pattern of regression of the posterior subcapsular cataract in the left eye 3 weeks after the initial presentation. (Reproduced with permission from Sharma, P, Vasavada, AR. J Cataract Refract Surg 27:789–794, 2001)

FIGURE 2.

Nonproliferative diabetic retinopathy with clinically significant macular edema.

(Reproduced with permission from The Wills Eye Manual: Office and Emergency Room Diagnosis and Treatment of Eye Disease, 5th edition; Ehlers and Shah, editors, Wolters Kluwer|Lippincott Williams and Wilkins, Philadelphia, 2008)

FIGURE 3. Proliferative retinopathy with disc vessels, gliosis, and traction retinal detachment superiorly. (Reproduced with permission from Naji, A. and Vernon, SA. J R Soc Med 96:266–272, 2003)

FIGURE 4.

Left eye. (Top) Late-phase fluorescein angiogram shows leakage from the optic nerve head with surrounding peripapillary hemorrhages. (Bottom) Late-phase fluorescein angiogram 2 weeks later shows almost complete resolution of leakage from the optic nerve head with decrease in the hemorrhages. Vision improved from counting fingers to 20/50. (Reproduced with permission from Al-Haddad, CE, Jurdi, FA, and Bashshur, ZF. *Am J Ophthalmol* 137:1151–1153, 2004)

FIGURE 5.

Right eye. (Top) Late-phase fluorescein angiogram shows leakage from the optic nerve head with counting fingers vision. (Bottom) Two weeks later, there is significant decrease in the leakage on the late-phase angiogram and improvement in vision to 20/40. (Reproduced with permission from Al-Haddad, CE, Jurdi, FA, and Bashshur, ZF. *Am J Ophthalmol* 137:1151–1153, 2004)

Table**Diabetic Retinopathy Disease Severity Scale**

Category	Findings observable on dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild nonproliferative diabetic retinopathy	Microaneurysms only
Moderate nonproliferative diabetic retinopathy	More than microaneurysms but less than severe nonproliferative and/or soft exudates, VB, IRMA to a mild degree
Severe nonproliferative diabetic retinopathy	IRMA present in 1 or more quadrants OR VB in 2 or more quadrants OR H/MA in 4 or more quadrants
Very severe nonproliferative diabetic retinopathy	Two or more conditions for severe nonproliferative diabetic retinopathy
Early poliferative diabetic retinopathy	Neovascularization of the disc or elsewhere which does not meet the high risk characteristics
High-risk proliferative diabetic retinopathy	Moderate or severe neovascularization on or within 1DD of optic disc (NVD) >1/4 to 1/3 disc area or mild new neovascularization on or within 1DD of optic disc (NVD) if fresh vitreous or preretinal hemorrhage OR moderate or severe new neo elsewhere (NVE) if fresh vitreous or preretinal hemorrhage

From: Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs: An extension of the modified Airlie House classification. ETDRS Report Number 10. Ophthalmology 98: 786–806, 1991

Table**Diabetic Macular Edema Disease Severity Scale**

Category	Findings observable on dilated ophthalmoscopy
Macular edema	Thickening of retina at or within 1DD of center of macula OR hard exudates within 1DD of center of macula with associated retinal thickening
Clinically Significant Macular Edema	Retinal thickening at or within 500 microns of center of macula OR hard exudates at or within 500 microns of center of macula if associated with thickening of adjacent retina OR zone(s) of retinal thickening 1 disc area in size at least part of which is within 1DD of center of macula.

From: Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs: An extension of the modified Airlie House classification. ETDRS Report Number 10. Ophthalmology 98: 786–806, 1991