Ocular Complications in Diabetes

M Rema, R Pradeepa

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CHAPTER OUTLINE

INTRODUCTION

Diabetes poses a major health problem globally and is one of the top five leading causes of death in most developed countries and substantial evidences suggest that it will reach epidemic proportions in developing and newly industrialized countries.[1] Complications of diabetes are the major cause of morbidity and mortality in persons with type 1 and type 2 diabetes. Although the pathogenesis differs in the two forms of diabetes, the pathophysiology of microvascular complications appears to be similar. Diabetes particularly affects tissues in which glucose uptake increases during hyperglycemia, leading to raised intracellular glucose concentration causing cumulative and progressive tissue damage in the retina through the summation of micro vascular occlusions.[2]

Of the many complications of diabetes, visual impairment is perhaps the most feared. Diabetic individuals are more prone to visual disability than those without diabetes. Eye disease represents an end-organ response to a generalized medical condition. All structures of the eye are susceptible to harmful effects of diabetes.[3]

In India with the epidemic increase in incidence of diabetes mellitus diabetic retinopathy is fast becoming an important cause of visual disability. In an epidemiological study conducted in urban South India, the Chennai Urban Rural Epidemiology Study (CURES), the overall prevalence of diabetes was 17.6%.[4] Visual disability from diabetes represents a significant public health problem and foremost attention has to be paid to the retinal complications of diabetes mellitus, as one in four diabetic subjects develop diabetic retinopathy (DR) in the Indian scenario. This chapter will discuss namely about the extra-retinal complications of diabetes mellitus (Table 1).

MEDIATORS AND MECHANISMS OF OCULAR DAMAGE IN DIABETES MELLITUS

Diabetes has wide ranging effects on metabolism which indicates that there are many potential mediators of ocular tissue damage in long standing disease, probably due to prolonged exposure to high glucose levels (hyperglycemia). Three hallmark international multicenter trials namely, the Diabetes Control and Complications Trial (DCCT)[5], the United Kingdom Prospective Diabetes Study (UKPDS)[6] and the Kumamoto trial[7] have demonstrated that intensive glycemic control helps to minimize/prevent diabetic eye complications. Currently four major biochemical pathways have been hypothesized to explain the mechanism of diabetic eye diseases all starting initially from hyperglycemia induced vascular injury which has been reviewed in a recent article.[8] These

Table 1. Ophthalmic Abnormalities of Diabetes Mellitus

Structure	Manifestations
EXTRA-RETINAL	
Orbit and Lids	Orbitorhinomucormycosis Orbital Cellulitis Chalazion Hordeolum externum (stye) Hordeolum internum Xanthelasma Blepheroptosis Blepharitis
Extraocular Muscles	Cranial nerve palsies • Third nerve palsy (oculomotor) • Fourth nerve palsy (trochlear) • Sixth nerve palsy (abducens) • Seventh nerve /bell's palsy (facial)
Conjunctiva	Microcirculation changes, Microaneurysms
Cornea	Generalized alterations Corneal Sensitivity
Iris And Pupil	Pupillary Abnormalities Generalized alterations Iris neovascularization
Angle Structures	Open-angle glaucoma Angle Closure Glaucoma Neovascular glaucoma (NVG)
Lens	Cataract formation Refractive changes
Vitreous	Asteroid Hyalosis Vireous contraction Posterior vitreous detachment
Optic Nerve	Papillopathy Anterior ischemic optic neuropathy (AION) Optic neuritis Optic atrophy
RETINAL	
Retina	Diabetic retinopathy Lipemia retinalis Retinal vein occlusion

mainly include i) enhanced glucose flux through the polyol pathway, ii) increased intracellular formation of advanced glycation end-products (AGE), iii) activation of protein kinase C (PKC) isoforms and iv) stimulation of the hexosamine pathway. Recent studies have suggested that these mechanisms seem to reflect a hyperglycemia induced process initiated by superoxide overproduction by mitochondrial electron transport chain.[9]

Increased polyol Pathway

In diabetic subjects with uncontrolled blood sugars, the activity of the polyol pathway non-insulin-dependent metabolic pathway of glucose is increased. This pathway consists of two steps, the reduction of glucose to sorbitol by aldose reductase and NADPH, followed by oxidation of sorbitol to fructose by sorbitol dehydrogenase and NAD+.[10] Sorbitol, which cannot be transported through the lens membrane accumulates in the lens tissue creating a hypertonic condition, to maintain osmotic equilibrium. This alters the membrane permeability resulting in the loss of several important molecules including glutathione, magnesium, and potassium.

Sorbitol accumulation in the lens and in the nerves seems to be an important factor in the development of cataract and in the slowing down of nerve conduction in diabetic individuals. However, the mechanisms may be different, aldose reductase-induced osmotic stress appears to be the causative mechanism of diabetic cataract, whereas aldose reductase-induced oxidative stress the rationale of neuronal dysfunction.[11] Sorbitol accumulation has also been observed in corneal epithelium, which may result in corneal abnormalities. Recent studies also suggest that the polyol pathway may play a role in early structural abnormalities of retinal microangiopathy. Cellular damage may occur due to increased production of glycating sugars, resulting in AGE formation, and/ or depletion of reduced glutathione, resulting in oxidative damage. The polyol pathway is a dream target in retinopathy treatment because excess aldose reductase activity has been proposed to be a mechanism for human diabetic retinopathy.[12] The long-term trial of Sorbinil - an inhibitor of aldose reductase, reported that it delayed the rate of progression of the number of microneurysms but did not prevent the worsening of diabetic retinopathy.[13]

Increase advanced glycation end-products (AGE) formation

Glucose can react with epsilon amino -group of lysine in the protein resulting in formation of an adduct. This process is called nonenzymatic glycation and it can occur at an accelerated rate in diabetes due to chronic hyperglycemia. This nonenzymic glycated protein undergoes a series of chemical modification resulting in Advanced Glycation End Products (AGEs).[14] AGEs can also arise from:

a. intracellular auto-oxidation of glucose to glyoxal
b. decomposition of the Amadori product (glucose derived 1-amino-1-deoxyfructose lysine adducts) to 3-deoxyglucosone and fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate to methylglyoxal.

The AGEs so formed can induce a variety of pathological changes which include damaging the structural proteins (collagen) and extracellular matrix components. These AGE-modified proteins bind to specific receptors - Receptor for Advanced glycation End products (RAGE) in the cell membrane of macrophages, endothelial cells and trigger a signaling cascade leading to the release of proinflammatory cytokines and adhesion proteins that favour thrombosis and eventually capillary occlusion. In addition, retinal endothelial AGE receptor binding appears to mediate increased vascular permeability, probably through the induction of vascular endothelial growth factor (VEGF).

AGEs play a vital role in the complex pathogenesis of basement membrane thickening in diabetic retinopathy and might have a role in the degenerative changes of the lens in diabetic patients . Increased levels of AGEs have been observed in both senile and diabetic cataractous lenses.[15] It is reported that in diabetic subjects accumulation of AGEs in the basement membrane, particularly laminin, may play a causative role in the corneal epithelial disorders.[16] Administration of antioxidants[17] have shown to partially prevent various functional and structural manifestations of retina in animal models but has not been successful in reducing the clinical manifestations of DR. Beneficial effects in the retinal vasculature of diabetic rats have also been observed with other inhibitors of AGE formation, including pyridoxamine and benfotiamine.[18] However, this could not be extrapolated to humans due to toxic effects and derivatives of it are being currently tried.

Increased Protein Kinase C (PKC) activation

The PKC family is a large group of structurally related enzymes that require for their activation, phosphatidylserine / diacylglycerol (DAG) / free fatty

acids and/or Ca^{2+} ions in addition to Mg^{2+}. PKC isoforms (especially α and δ) are activated by the lipid second messenger DAG, synthesized de novo from increased intracellular glucose, leading to decreased tissue blood flow by reducing production of nitric oxide (potent vasodilator). PKC also enhances vascular permeability and neovascularization in the eye through expression of VEGF. Strategies to block formation of VEGF by intravitreal injection has been tried because systemic anti VEGF factors would have clinical disadvantages as the formation of new blood vessels is beneficial to other areas with diabetic vasculopathes as the coronary bed and the lower limbus.[19] Increase in PKC levels has been shown to alter many cellular functions including alterations in collagen synthesis, action of stimulating hormones and growth factor receptor recycling. Activation of PKC also alters the expression of endothelium-derived vasoactive factors such as the potent vasoconstrictor peptide endothelin-1 (ET-1), which has been identified in many retinal cells such as the capillary endothelial cells and pericytes[20] leading to vasoconstriction and retinal ischemia.

Heilig et al[21] have demonstrated that the inhibition of hyperglycemia-induced superoxide in mice prevents diabetes-induced activation of the PKC pathway. The β isoform of PKC has been identified to be specific to diabetic retinopathy and the inhibition of this isoform of PKC has been shown to block the VEGF mediated processes.[22] PKC β inhibitors have been tried in severe nonproliferative diabetic retinopathy[23] and macular edema[24] but have not been advocated yet for clinical practice. Recently the safety and efficacy of the orally administered PKC β isoform-selective inhibitor ruboxistaurin (RBX) has been evaluated by the PKC-DRS study group in subjects with moderately severe to very severe NPDR.[23] The study showed that RBX was well tolerated and reduced the risk of visual loss but DR progression may not be significantly reduced. The effect of another PKC inhibitor, PKC412 orally administered at doses of 100 mg/d or higher was studied and reported that it may significantly reduce Diabetic Macular Edema (DME) and improve visual acuity.[24]

Hexosamine pathway

Activation of the hexosamine pathway by hyperglycemia may result in various changes in both gene expression and in protein function that together contribute to the pathogenesis of diabetic vascular complications. This pathway is also one of the possible mechanisms involved in diabetic keratopathy. Recently studies have reported that hyperglycemia could cause diabetic vascular complications by shunting glucose into the hexosamine pathway leading to hyperglycemia-induced and lipidemia induced insulin resistance and induction of synthesis of growth factors.[25] Nakamura et al[26] have demonstrated that the excessive glucose flux through the hexosamine pathway may direct retinal neurons to undergo apoptosis in a bimodal fashion and highlights that this pathway may be involved in retinal neurodegeneration in diabetes.

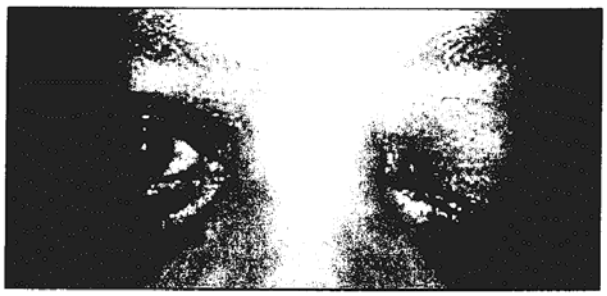

Fig. 1a. Orbitorhinomucormycosis of the left eye showing ptosis and periorbital swelling

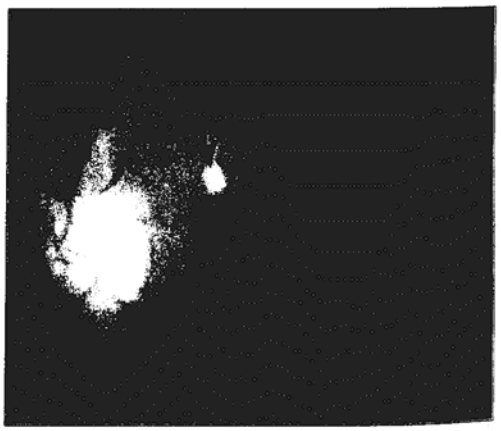

Fig. 1b. Colour photo of the Left eye: Fundus picture shows cotton wool spots with disc pallor

EXTRA-RETINAL OCULAR MANIFESTATIONS

Individuals with diabetes are generally prone to infections of any kind and at any site predisposing them to acute infections, which is normally of bacterial origin in the orbit and eyelids.

ORBIT

Orbitorhinomucormycosis

Mucormycosis is a rare opportunistic infection caused by fungi of the family Mucoracae, which characteristically affects diabetic patients with ketoacidosis or immunosuppression.[27] This aggressive and fatal infection acquired by inhalation of spores, gives rise to upper respiratory infection, which then spreads to the contiguous sinuses and subsequently to the orbit and the brain. Mucormycosis presents with gradual-onset of facial and periorbital swelling, ptosis, diplopia and visual loss which may lead to complications such as retinal vascular occlusion, multiple cranial nerve palsies and cerbrovascular occlusions.

Figure 1a shows a 55-year old woman with orbitorhinomucormycosis. The left eye presented with periorbital swelling,complete ptosis, proptosis and external ophthalmolplegia. Fundus examination showed multiple cotton wool spots with disc pallor in the left eye (Figure 1b).

Treatment of Orbitorhinomucormycosis includes management of acidosis and aggressive surgical intervention under amphotericin B administered both systemically and locally. Wide excision of devitalized and necrosed tissue with correction of underlying metabolic effects, is the only practicable mode of intervention.

Orbital Cellulitis

This condition is commonly seen in diabetes from any focus of infection in the body. Bacterial orbital cellulitis is a life threatening infection of the soft tissue behind the orbital septum. It may be caused by the extension of preseptal cellulitis which may be sinus-related in some cases, local spread from adjacent dacryocystitis, mid facial or dental infection, hematogenous spread or following retinal, lacrimal or orbital surgery. Orbital cellulitis presents with severe malaise, fever, pain, visual impairment, unilateral, tender, warm and red periorbital and lid edema, proptosis, painful ophthalmoplegia and optic nerve dysfunction.[28]

To manage this condition a) identify focus of infection and treat suitably, b) optic nerve function should be monitored every 4 hours, steroids should be used under cover of antibiotics and c) surgical intervention should be considered if, there is poor response to antibiotic therapy. Decreasing vision, orbital or subperiosteal abscess and an atypical picture, may merit diagnostic biopsy.

Fig. 2. Chalazion in the upper lid of the left eye

Lids

Chalazion

Chalazion (meibomian cyst) is a chronic, sterile, lipogranulomatous inflammatory lesion caused by blockage of meibomian gland orifices and stagnation of sebaceous secretions.[29] Chalazion is a painless, round, smooth swelling within the tarsal plate of variable size which may be multiple or bilateral. Management of chalazion requires incision and curettage under cover of antibiotics and good glycemic control. In an acute stage, topical and systemic antibiotics may be required before incision. Figure 2 shows a 40 year women presenting with chalazion on left lateral upper lid.

Hordeolum externum (stye)

Stye is a suppurative inflammation of one of the Zeis glands caused by staphylococcus. Pain along the lid margin is followed by a swelling, which characterizes it from chalazion where swelling is painless, unless infected. The gland becomes hard, swollen and tender subsequently forming an abscess. Multiple lesions may also be present. Hordeola are found more frequently in persons who have uncontrolled diabetes, chronic blepharitis, seborrhea and increased serum lipids. Application of antibiotic ointment prevents recurrences. Hot compresses and epilation of the lash associated with the infected follicle may hasten resolution.

Fig. 3. Xanthelasma on the medial upper and lower lids

Fig. 4. Scurf, or debris, found amid eyelashes in patient with blepharitis

Hordeolum internum

Hordeolum internum is an abscess caused by an acute staphylococcal infection of the meibomian gland. It is a tender, painful swelling within the tarsal plate, occurring less frequently but presents as a more violent inflammation than the stye. The lesion may enlarge and then discharge either posteriorly through the duct or through the conjunctiva. An incision and curettage may be required if a residual nodule remains after the acute infection has subsided after treatment with suitable antibiotics.[29]

Xanthelasma

This condition occurs more frequently in diabetic patients with elevated serum lipid levels, but does not pose a threat to vision. Xanthelasma does not occur as a result of diabetes per se, but may reflect poor diabetic control.[27] It is a yellowish, subcutaneous plaque consisting of cholesterol and lipids which are usually located at the medial aspects of the eyelids. Destruction with carbon dioxide or argon laser is preferred to excision for cosmetic reasons. However, recurrences are possible if the disturbance in lipid metabolism persists. Figure 3 illustrates xanthelasma on the medial part upper and lower lids of a 32 year old male subject.

Blepheroptosis

Ptosis is an abnormally low position of the upper lid which may be unilateral or bilateral, partial or complete, congenital or acquired. The various causes for this condition include innervational defect such as third nerve palsy and oculosympathetic palsy (neurogenic), myopathy of the levator muscle itself or neuromyopathic (myogenic), defect of the levator aponeurosis (aponeurotic) or gravitational effect of a mass or scarring(mechanical). No alterations occur in the pupil, unlike in other third nerve palsies. The degree of lid closure is influenced by duration of diabetes and is considered to be more prevalent in type 1 diabetic individuals particularly in those with retinal involvement.[30]

The management of ptosis is variable, consequent to the causes. In neurogenic ptosis, patient should be treated on conservative lines for 6-9 months. Myogenic ptosis responds to corticosteroid, immunosuppressive therapy, plasmapheresis and thymectomy. In aponeurotic and mechanical ptosis, the deformity is usually corrected by surgery.

Blepharitis

Chronic blepharitis is common in diabetic patients due to uncontrolled hyperglycemia, reflecting general proneness to infections. This condition is a chronic inflammation of the lid margin. Clinically it occurs in two forms, squamous and ulcerative blepharitis. Squamous blepharitis is characterized by the appearance of fine whitish scales around the roots of lashes, which can be easily removed without ulceration. While in ulcerative blepharitis, the lid margins are ulcerated and infection is more deeply seated and involves the hair follicles destroying some and distorting others in the process. If untreated the ulceration may extend to involve the whole lid margin and the inevitable sequelae of fibrosis leads to deformities of the lids. Scurf, or debris, found amid eyelashes in a male patient with blepharitis (Figure 4).

Management of blepharitis consists of appropriate removal of the crust, application of specific antibiotic ointment depending on the sensitivity of the organism and massage of the lid margin. Systemic tetracyclines

and mechanical expression of the meibomian glands are the mainstay of treatment for squamous blepharitis.

Lacrimal Glands

Hyperglycemia can affect the nerves supplying the lacrimal gland. Diabetes has been reported to affect the lacrimal gland by decreasing tear secretion, forming a less uniform lipid layer and reducing tear breakup time.[31] Rubinstein et al reported that tear secretion is reduced only in type 2 subjects though the effect of age needs consideration.[32] Patient presents with complaints of dry eyes leading to irritation. As a sequel of lack of tears, the patient is at a higher risk of developing corneal ulcers hence, proper lubrication using tear substitutes should be advised.

CONJUNCTIVA

Microcirculatory changes occur in diabetic individuals, which are a reflection of general microvascular disturbance of diabetes.[33] Conjunctival microcirculation changes may manifest as microaneurysms, vasoconstriction, diurnal variation in venous dilation, vessel distension, increased touruosity, fusiform dilatation, arteriole wall thickening, sludging of blood in vessels and capillary proliferation. Microaneurysms are often seen adjacent to the limbus and occasionally can be observed in non-diabetic individuals also. The diurnal variation in venous dilatation is independent of blood glucose level or time of insulin therapy.[34]

The conjunctival alterations are more common in adult diabetic individuals suggesting that the vasculature becomes more susceptible with age. In contrast in a study conducted in pediatric diabetic patients conjunctival microabnormalities existed in all pediatric type 1 diabetic subjects in varying degrees despite their relatively young age.[35] Isenberg et al[36] have reported that conjunctival oxygen tension in diabetic patients had significant correlation with the level of conjunctival hypoxia and the degree of retinal involvement.

CORNEA

Generalized alterations

Diabetes has impact on every layer of the cornea and is often more susceptible to injury and heals more slowly in diabetic individuals than the normal individuals. The sorbitol pathway is believed to be an important factor in some corneal manifestations of diabetes. It has a significant effect on morphological, metabolic, physiological, and clinical aspects of the cornea. Morphological changes occur in the corneal epithelium, epithelial basement membrane and basement membrane complexes, stroma, and endothelium. Myriad primary and postoperative manifestations are caused due to the homeostasis of these structures in both the non-stressed and the stressed cornea . The corneal epithelium may exhibit changes including a decrease in the number of cells, thinning and basement membrane alterations affecting epithelial adherence and epithelialisation. Clinically, this can lead to many diabetic patients having epithelial keratitis. Corneal epithelial lesions can be observed in approximately one-half of asymptomatic patients with diabetes mellitus. Recent studies suggest that the polyol pathway may play a role in the pathogenesis of these disorders.[37]

Corneal complications such as tear film dysfunction, elevated glucose in tears, neurotrophic ulcers, corneal edema, wrinkles in Descemet's membrane and decrease in corneal sensitivity have also been reported in diabetic individuals.[34] Type 2 diabetic individuals when compared with the healthy control group, showed decreased tear film break up time, increased rate of staining with fluorescein sodium on the cornea and abnormal conjunctival epithelium.[38]

In the experimental scenario changes were observed in the morphologic features of the collagen within Descemet's membrane in diabetes induced rats.[39] Minute folds in Descemet's membrane probably represent an alteration in the tissue fluid level of the cornea. These folds increase with age in both normal and diabetic subjects, with female diabetic subjects being more prone. Little is known about the effects on corneal stroma. Some studies have reported stomal edema following vitrectomy to be associated with diabetes but others dispute this statement.

In addition to the morphological changes in the epithelium and endothelium, an increase in corneal thickness in diabetic individuals has also been reported.[40] This change may be observed early in the course of the disease and related to severity of the retinal involvement.

Corneal Sensitivity

Studies have demonstrated that diabetic individuals have decreased corneal sensitivity[41], making them more vulnerable to corneal trauma. The reduction in sensitivity is part of the diabetic peripheral neuropathy and due to inactivation of the trigeminal nerves and their branches in the cornea,

which in effect increases the conduction time. It also decreases tear secretion, which in turn increases tear film osmolarity and reduces goblet cell density. The other factors involved in the pathogenesis are accumulation of sorbitol within the lamellae of the Schwann cell, causing mechanical compressive or toxic damage to the axon and partial demyelination of the nerve due to abnormal lipid metabolism.

Studies have clearly demonstrated the existence of neuropathy in diabetic cornea, both in an animal model and in the humans.[35] Diabetic keratopathy has been thought to represent a form of corneal neuropathy, which emerges subsequent to the undue stress like intraocular surgery or photocoagulation. These lesions are transient and clinically resemble the keratopathy seen in staphylococcal keratoconjunctivitis. The morphology of corneal nerves has been found to be altered in diabetic rats and humans.[42] These morphological alterations are probably implicated in the development of neurotrophic corneal ulcerations with diabetes.

Measurement of corneal sensitivity may be a useful tool in the early diagnosis of diabetic neuropathy. Ruben et al measured corneal sensitivity in diabetic patients undergoing photocoagulation for proliferative retinopathy and reported that both type 1 and type 2 diabetic individuals showed significantly decreased sensitivity and that there was no significant change following photocoagulation.[43] Decreased corneal sensitivity contribute to a host of complications observed in the epithelium of the diabetic individual including recurrent erosions, slowed wound repair, predisposition to abrasions, neurotrophic corneal ulceration, transient punctuate diabetic keratopathy, epithelial desquamation and defective re-epithelialisation. In established cases, re-epithelisation should be promoted by use of lubricants and patching. Newer treatment modalities include use of topical nerve growth factor[44], aldose reductase inhibitor CT-112[45] and amniotic membrane transplantation.[46]

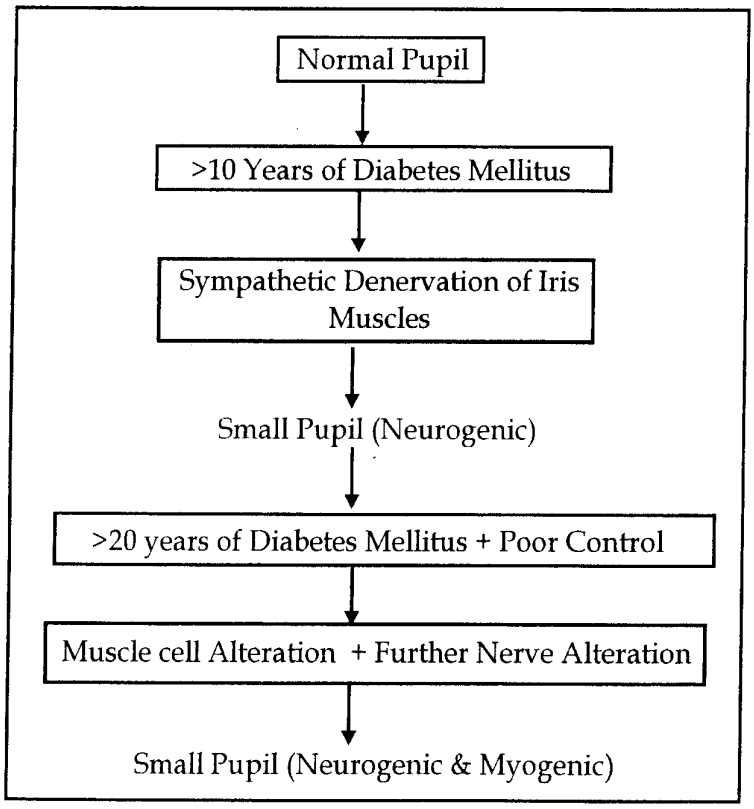

Fig. 5. The sequence of events in pupillary dysfunction in diabetes mellitus (Ref 47)

PUPIL AND IRIS

Pupillary Abnormalities

The pupillary abnormalities in diabetic individuals include decreased light reflexes both at the onset and during the course of diabetes mellitus, decreased hippus during continuous illumination and increased miosis or failure to dilate normally in the dark. Some diabetic pupils resemble the Argyll Robertson syndrome (non-syphilitic) and dilate poorly with anti-muscarinics but exhibit supersensitivity with sympathomimetic drugs.[47] These pupillary dysfunctions are closely associated with long duration and poor control of diabetes, and accounted for by either myopathy or neuropathy, or maybe both. The sequence of events in pupillary dysfunction in diabetes mellitus described by Alio et al[47] is summarized in Figure 5.

Other speculated causes for pupillary dysfunctions reported include rigidity of iris and distension of the pigment epithelium from the formation of vacuoles. Both these are inferred from the observation that the pupil motility depends on the glucose levels.

Generalized alterations

Hyperglycemia can also cause proliferation of the iris pigments causing melanosis of the iris and overgrowth of the posterior pigment epithelium that extends over the edge of the pupil in the margin area forming an apron known as 'ectropion uveae'. These conditions are normally a sequel to iris neovascularization although it has been observed in cases without rubeosis also. Diabetic subjects are also predisposed to moderate to severe iritis, in which inflammation primarily affects the iris. It is characterized by a thick plastic exudative discharge with a tendency for bleeding from the iritis causing hyphema.[48]

Iris neovascularization

Diabetic individuals are prone to both morphologic and vascular alterations. Iris neovascularization (rubeosis iridis) is known to occur due to frequent occlusion of small vessel elements. It develops as tiny dilated capillary tuffs or red spots around the pupillary margin and may be missed unless examined carefully under high magnification. The new vessels grow radially over the surface of the iris towards the angle, sometimes joining dilated blood vessels at the collarette. At this stage intraocular pressure (IOP) may be still normal in some cases and the new vessels may regress either spontaneously with good metabolic control and panretinal photocoagulation of the retina.[49]

Rubeosis is common in individuals with advanced diabetes with invariable proliferation of blood vessels in the retina and it has been estimated that less than 5% of individuals with retinal proliferation who are not laser treated may develop this condition.[49] Neovascular glaucoma may eventually develop which is a painful and vision debilitating condition. Many studies have reported regression of neovascularization of iris following panretinal photocoagulation or by repair of a detached retina.

ANGLE STRUCTURES

Open-angle glaucoma

Open angle glaucoma has reported to be two times more common in diabetic subjects than in the general population.[50] The pathologic mechanism leading to this condition is microscopic blockage of the trabecular meshwork. Open-angle glaucoma is an asymptomatic, progressive optic neuropathy characterized by enlarging optic disc cupping and visual field loss. The Blue Mountain Eye Study reported that the prevalence of open-angle glaucoma was increased in people with diabetes and ocular hypertension (elevated intraocular pressure in the presence of normal optic discs and visual fields) was also more common in diabetic individuals.[51]

Management of open-angle glaucoma in diabetic individuals includes a complete workup and then treating by topical and systemic hypotensive agents taking into view their general medical condition. Early detection of optic nerve damage can be efficiently assessed by computerized visual fields charting and using newer imaging techniques like Ocular Coherence Tomography (OCT). The OCT depicts cross-sectional image and can accurately assess the thickness of Retinal Nerve Fibre Layer (RFNL), optic cup disc ratio and peri papillary rim of the optic disc.

Angle Closure Glaucoma

Diabetes may be associated with angle closure glaucoma due to an increase in lens thickness in diabetic patients and autonomic dysfunction which may lead to a more dilated pupil.[52] This form is comparatively rare among persons with diabetes . It presents with severe pain, reduced visual acuity, congestion of the globe , increased IOP, corneal edema and aqueous flare due to leakage of proteins from the iris new vessels. Management is aimed mainly at

relieving pain. Medical management is with systemic or topical hypotensive agents except miotics. Visual acuity recovers with medical treatment.

Neovascular glaucoma (NVG)

Neovascular glaucoma (NVG) from diabetes, although not nearly as common, inflicts devastating consequences on vision and is a serious condition occurring as a result of iris neovascularization . The leading cause of NVG is retinal vein occlusion, which accounts for 36% of all cases. Diabetes is the second in frequency accounting for 32% of all cases and 95% of bilateral cases.[53] Those with longstanding diabetes (>10 years), proliferative retinopathy and cataract have higher risk of developing NVG. Due to the increase in prompt application of panretinal photocoagulation, the prevalence of NVG is decreasing.[49]

LENS

The changes that may occur to the diabetic lens are (i) the formation of cataracts and (ii) alterations to its curvature and refractive index which result in refractive changes (dynamic changes).

Cataract formation

Cataract is more prevalent and occurs at a younger age in diabetic individuals than in the general population. Peterson et al[54] have demonstrated that cataract is observed 15-25 times higher in diabetic patients under 40 years of age. It is a major cause of visual impairment and blindness, particularly in type 2 diabetes. The overall risk of cataract formation for all ages is 2-4 times greater in the diabetic subjects than in the non diabetic subjects.[55] Posterior subcapsular cataract is particularly common in diabetic patients than other morphological types of cataract.[56]

Longer duration of diabetes, poor metabolic control, increased severity of retinopathy, older age at examination and diuretic usage in type 1 patients results in higher prevalence of cataract whatever age at examination. Increased severity of retinopathy, diuretic usage, lower intraocular pressure, smoking and lower diastolic blood pressure in type 2 patients were significantly associated with higher prevalence of cataract.[55]

Typically, these are snowflake opacities, polychromatic crystals and vacuoles in the lenticular cortex. The cataract can progress rapidly until the whole lens is cloudy, or reverse with appropriate treatment. The two types of cataract in diabetic individuals are (i) true diabetic and (ii) the senile type cortical cataracts. The general mechanism of both types of cataracts is related to sorbitol pathway. The 'snowflake' or 'juvenile diabetic' cataract characteristic of poorly controlled type 1 diabetes is very uncommon. These cataracts are bilateral, and rarely affect the vision. They often have a rapid onset, appear as white punctate or stellate opacities, and can resolve without treatment.

The senile type of cataract in the diabetic patient is identical and clinically alike in appearance as presented in the aged population. The rapidity of development is remarkable, especially with uncontrolled severe hyperglycemia. Dense cataracts often preclude a proper examination of retina which may result in undiagnosed vision threatening retinopathy.

Cataract surgery (phacoemulsification and intracapsular implantation of an intraocular plastic lens) is often effective in both cases, but may be compromised by co-existent retinopathy and postoperative complications including anterior-chamber inflammation and posterior capsule opacification.[57] Of patients undergoing surgery for senile type of cataract, 4.2% were found to be undiagnosed diabetic patients as reported by Caird et al.[58] Rema et al[59] have shown that 44% of type 2 diabetic subjects had progression of DR after extra capscular cataract extraction and IOL implantation. In a few diabetic subjects DR was diagnosed for the first time after cataract surgery i.e. 7 of 88 eyes that were not known to have retinopathy preoperatively.

Refractive changes

The dynamic alterations including changes in lenticular status either hydration or dehydration, as a result of changes in the osmolality of the aqueous from either a rise or fall in blood glucose and the shape of lens and/or its refractive index, results in fluctuating refractive errors and variable vision. These sudden refractive shifts are frequently the presenting symptom for a newly diagnosed diabetic person. Acute, severe or even moderate hyperglycemia may cause this shift either towards hyperopia (transient nature) or myopia (more permanent nature). Many studies have reported that hyperopic shift is more common than the myopic one.[60] Transient refractive changes are commonly seen and may persist for a few weeks. Myopia may be due to an increase in thickness and curvature of the crystalline lens that occurs in diabetic patients, which is reversed after control of diabetes. Sometimes on intensive control with insulin

there is a tendency towards hypermetropia following institution of therapy. The change in the refractive error is probably due to the alteration in the aldose reductase/sorbitol pathway.

EXTRAOCULAR MUSCLES

Cranial nerve palsies

Cranial nerve palsies are some dramatic complications in uncontrolled diabetes. Presentation of such neuropathy, however, is of serious concern to the individual, because the presenting symptom is usually disturbing diplopia occasionally accompanied by pain in the eye. Cranial nerve palsies usually occur in isolation but can be seen as a multiple presentation and interestingly, diabetic cranial neuropathies are exclusively seen in adults. The cause of cranial neuropathies in diabetic patients is thought to be a combination of vascular and metabolic problems leading to a disruption of axonal transport and vascular permeability.[61]

Third nerve palsy (oculomotor)

The III Cranial nerve innervates the pupil, levator palpebrae, inferior and superior and medial rectus muscles. Diabetes affects the vasa nervosum which runs in the centre of the nerves, occasionally leading to occlusion of vasa nervosum. This occlusion affects the central nerve fibers sparing the superficial pupillary fibers, thus resulting in "pupil sparing III nerve palsy". It is often associated with periorbital pain or ipsilateral headache which may occasionally be the presenting feature of diabetes.[62] Diabetes-associated third-nerve palsy is manifested by unilateral ptosis and exotropia. The patient has bizarre defects in ocular mobility including elevation of upper eyelid on attempted adduction or depression in the affected eye. The pupil is spared in diabetes related occulomotor palsies, however, other causes have to be ruled out by a complete neurological examination and perhaps CT and MRI scans.

Fourth nerve palsy (trochlear)

This condition is rare when compared to III nerve palsy. The IV Cranial nerve supplies the superior oblique muscle. Although the most common cause of trochlear palsy is trauma, it can also be affected in diabetes, hypertension, tumors, vascular lesions, multiple sclerosis and meningitis. A patient with a trochlear nerve palsy typically has a vertical diplopia, worse on gaze away from the affected eye and at near. A torsional component may also be present (excyclotorsion). The patient usually adopts a contralateral head tilt to correct diplopia and bilateral involvement is common. Park's three step test and Double Maddox rod test are useful in defining the extent of palsy. Diplopia charting and Hess charting can be done to determine the severity of diplopia.[62]

Sixth nerve palsy (abducens)

In abducens nerve palsy, there is a horizontal diplopia, worse on gaze to the affected side and with distance vision. There is a limitation of abduction of the eye in question and the patient may exhibit a tilt of the head to the affected side to minimise diplopia.[62] Movement of the eye laterally past the midline is restricted or absent. The onset may be sudden and there is neither visual loss or visual field loss. The sixth nerve has a long intracranial course and multiple causes of palsy necessitating careful neurological evaluation). A retrospective population-based case-control study of patients with new onset of neurologically isolated sixth nerve palsy concluded that there is a 6-fold increase in odds of having diabetes in cases of sixth nerve palsy over controls.[63]

Seventh nerve / bell's palsy (facial)

Bell's palsy, an idiopathic facial nerve palsy, is the most common cause for acute facial nerve paralysis and diabetic patients are four times more likely to develop this condition.[64] Patients with a facial nerve palsy present with a weakness on one side of the face.

Clinical features depend upon the level of lesion (Lower motor neuron or Upper motor neuron) and whether one or both facial nerves are affected. The lower motor neuron lesion presents with weakness of all muscles of facial expression, deviation of angle of mouth, dribbling of saliva on the affected side, deepening of nasolabial fold, weakness of frowning (frontalis muscle) and eye closure (orbicularis oculi muscle) and signs of corneal exposure. There may be loss of taste on anterior 2/3rd of tongue in some lesions. Upper motor neuron lesion presents with weakness of lower half of face on opposite side of lesion with sparing of frontalis and orbicularis oculi muscles.

The prognosis for cranial nerve palsies is good, with function usually being restored over a period of 6-9 months. Nerve palsies that do not resolve after approximately six months are most probably not of diabetic origin. Physiotherapy is the mainstay of management of cranial nerve palsies. Non surgical management includes use of Fresnel prisms if the angle of deviation is small, uniocular occlusion to avoid diplopia. In case of abducens palsy, botulinum

toxin injection may be injected into the uninvolved lateral rectus muscle to avoid contracture before the deviation improves/stabilizes. Surgical management is usually not earlier than six months from the date of onset.[62] Trochlear nerve palsy usually recovers completely within 6-8 months. A careful orthoptic evaluation should be made, followed either by superior oblique strengthening, inferior oblique weakening or classical Harada Ito procedure. In case of facial palsy, the commonly employed, treatment modalities include eye patching and lubrication to protect the cornea.[65] In non-resolving type of facial palsy, tarsorraphy or medial canthoplasty may be done as a permanent procedure. Steroids are generally agreed to be beneficial in facial palsy.[66]

Diabetes can also affect autonomic nerve function. The most common clinical manifestation in the eye is an exaggerated miosis from a lack of sympathetic tone. Parasympathetic dysfunction can lead to a more dilated pupil. The diabetic patient may have light-near dissociation, where the pupil's near reflex is greater than the light reflex. Bilateral light-near dissociation is usually seen in type 1 diabetic subjects, although may also be seen in type 2 diabetic patients of long duration. This occurs due to pupillary autonomic denervation[67] and may represent a selective neuropathy involving pupillomotor parasympathetic nerve fibers. Amplitudes of accommodation may also be reduced.[61]

VITREOUS

Asteroid Hyalosis

This condition is characterized by small but striking, highly refractile 'stars' (asteroids) in the vitreous. It appears as cream-white spherical bodies distributed throughout the vitreous either randomly or in chains or sheets. It rarely causes any visual symptoms and are usually found on routine examination. Opacity studies suggest that asteroid hyalosis are composed of calcium soaps together with various lipoids. They are usually unilateral (in 75% of cases) and occur mostly in elder persons and are said to be common in males than females. This condition is reported to be common in diabetic individuals, according to earlier reports.[68] It has been stated that 5.4% of the diabetic individuals have these bodies .Yazar et al have demonstrated that asteroid hyalosis can also cause artefactual lowering of axial length measurement, leading to significant error in calculations of intraocular lens power.[69]

Vitreous contraction

Instability of the vitreous is caused due to loss of gel state without dehiscence at the vitreoretinal interface, which may induce traction of the vitreous in cases of proliferative diabetic retinopathy (PDR). Viterous body consists of hyaluronic acid, which can change its configuration as a result of ionic interactions causing swelling and shrinkage of the vitreous, which eventually results in structural and volumetric alterations in the vitreous. These alterations will produce traction upon the structures which are attached to the vitreous cortex such as the new vessels present in PDR and contribute to progression of retinopathy either by traction on the new vessels or by inducing a rupture of the new vessels causing a vitreous hemorrhage.

Liquefaction/Posterior vitreous detachment

Posterior vitreous detachment (PVD) is a phenomenon, which occurs from degenerative changes in the vitreous and is significantly more common in diabetic subjects, even in eyes without retinopathy[70]. Pischel et al[71] reported that this condition is present in 60% of all patients over 50 years of age. Normally there is no effect on visual acuity, but the patient experiences a brief episode of photopsia. Clinically, acute bilateral occurrence of PVD is generally rare.

OPTIC NERVE

Optic nerve dysfunction may present itself in various clinical characteristics including optic disc swelling (diabetic papillopathy), optic atrophy, optic neuritis and ischemic optic neuropathy (Anterior ischemic optic neuropathy (AION) and Non- arteritic AION). In a study conducted in diabetic patients, ischemic optic neuropathy was the predominant form of optic nerve lesions (59.20%) followed by secondary optic atrophy, post ischemic optic neuropathy (33.40%) and retrobulbar optic neuritis (7.40%).[72]

Papillopathy

Diabetic paplillopathy is an uncommon condition characterized by transient visual dysfunction coupled with optic disc swelling occurring in both type 1 and type 2 diabetic subjects. It generally affects the type 1 diabetic individuals in the second and third decade who have diabetes for over 10 years. The etiology is unknown but theories postulate that retinal vascular leakage into and surrounding the optic nerve and disruption of axoplasmic flow resulting from micro vascular disease of the optic nerve head vasculature

may be responsible for this condition.[73] In most cases, the papillopathy is bilateral (50% of cases) and is thought to be a manifestation of ischemia. When severe, it is very similar in appearance to papilledema caused by raised intracranial pressure. Any loss of vision, which is usually moderate at worst, tends to recover in about six months. Prognosis is relatively good despite lack of specific treatment. In most cases spontaneous resolution occurs within several months, with stabilization or improvement of visual acuity, although mild optic atropy may still develop.

Anterior ischemic optic neuropathy (AION)

Anterior ischemic optic neuropathy (AION), one of the most common and visually crippling diseases in the middle-aged and elderly, is due to acute ischemia of the optic nerve head. AION is defined as segmental or generalized infarction within the prelaminar or laminar portions of the optic nerve caused by occlusion of short posterior ciliary arteries. Clinically, AION is of two types: (1) arteritic AION caused due to giant cell arteritis and (2) nonarteritic AION caused due to other risk factors.[74] AION affects diabetic patients of all ages. Diabetic subjects are more prone to develop bilateral AION.[75]

Arteritic AION

Arteritic AION associated with temporal arteritis is an ophthalmic emergency because this condition is likely to cause rapid, visual disability, which is almost always preventable if treated immediately.[74] In untreated patients the incidence is 30-50%, of which one-third develop bilateral involvement. This disease has a predilection for medium sized and larger arteries, particularly the superficial temporal, ophthalmic, posterior cillary and proximal part of the vertebral. Prognosis is very poor as visual loss is usually permanent although, very rarely, administration of large doses of systemic corticosteroids may be associated with partial visual recovery. Management involves taking a temporal artery biopsy and ESR and supporting with anti-inflammatory drugs.

Non-arteritic AION

Non-arteritic anterior ischemic optic neuropathy (NAION) refers to an idiopathic ischemic process of the anterior portion of the optic nerve. The typical presentation is sudden and painless visual loss, relative afferent pupil defect, a pale swollen optic disc and an inferior altitudinal hemianopsia.[76] Visual loss is frequently discovered on awakening, suggesting that nocturnal hypotension may play an important role[77]. The other associated risk factors include altered optic disc morphology, advanced age, hypertension, diabetes mellitus, hypercholesterolemia, collagen vascular disease and cataract surgery. It has been observed that 24% of subjects in the Ischaemic Optic Neuropathy Decompression Trial Study had diabetes.[78] Currently, there is no effective long-term treatment for this condition, although any underlying systemic factors should be treated and reduction of risk factors such as smoking should be encouraged.[62,76] About 40% of the patients may have some improvement in central vision. There is approximately 30-50% chance of the fellow eye getting affected. However, recurrence in the same eye is very rare.[62] It is also important to differentiate it from the arteritic type to aid management.

Table 2. Risk Factors Associated with the Development of Diabetic Retinopathy

Systemic factors	Ocular factors
Age	Posterior Vitreous
Sex	Detachment
Duration of diabetes	Old chorioretinopathy
Poor glycemic control	Cataract surgery
Hypertension	
Pregnancy	
Renal disease	
Raised triglycerides and hematocrit	
Smoking	
Alcohol	
Obesity	

Optic neuritis

Optic neuritis is one of the most common causes of sudden vision loss in the young subjects and occurs with higher frequency in diabetic individuals. This condition is an inflammatory, infective or demyelinating process affecting the optic nerve. The hypothesized etiological classification is outlined as i) demyelinating - the most common cause, ii) parainfectious - following a viral infection or immunization, iii) infectious – may be sinus related or cat-scratch fever, syphilis, Lyme disease, cryptococcal meningitis in AIDS patients and herpes zoster and iv) autoimmune - associated with systemic autoimmune diseases.[62] In diabetic subjects, along with autoimmunemechanism, ischemia and

Table 3. Diabetic Eye Examination Schedule

Type of Diabetes	Recommended Initial Eye Examination	Routine Minimum Follow-up*
Type 1	5 years after onset or during puberty	Yearly
Type 2	At time of diagnosis of diabetes	Yearly
Pregnancy in preexisting diabetes	Prior to conception or early in first trimester	3 months or more frequently as indicated by the physician 6 weeks postpartum

* Abnormal findings necessitate more frequent follow-up examinations.

nutritional deficiencies are also implicated.[79] Usually it affects only one eye, but may be extensive involving the chiasma and even the adjacent brain tissue.

Clinical features of demyelinating optic neuritis include subacute monocular visual impairment and may be discomfort in and around the eye, which often worsens due to movement of the eye. In some patients, frontal headache and tenderness of the globe are observed. Colours may appear "washed out". In parainfectious type, presentation is usually 1-3 weeks following a viral infection or immunization, frequently affecting more children than adults.

Management is probably not essential if visual loss is mild. The pain and discomfort due to this condition recedes after a few days. The vision usually improves in about 85% of patients after a period of weeks or even months.[79] However, when visual loss is severe and bilateral involvement is observed, intravenous steroids can be considered. It has been demonstrated in the Optic Neuritis Treatment Trial (ONTT) that there may be better and faster improvement in patients treated with intravenous steroids, especially in those who have extensive disease.[80] It has to be followed by oral steroids. Initiating therapy only with oral steroids can lead to deleterious effects.

Optic atrophy

Optic atrophy often results from arterial blood flow insufficiency associated with some systemic vascular disease (cardiovascular disease, hypertension, or diabetes mellitus). The lack of adequate blood perfusion pressure can create conditions leading to anoxia and death of the nerve fiber layer with a resultant visual field defect.[81] It usually occurs as a sequel of AION, optic neuritis, severe ischemia, internal carotid disease, central retinal artery occlusion, and retinal artery branch occlusion. As all these conditions are more common in diabetic patients, they are at higher risk of developing optic atrophy.

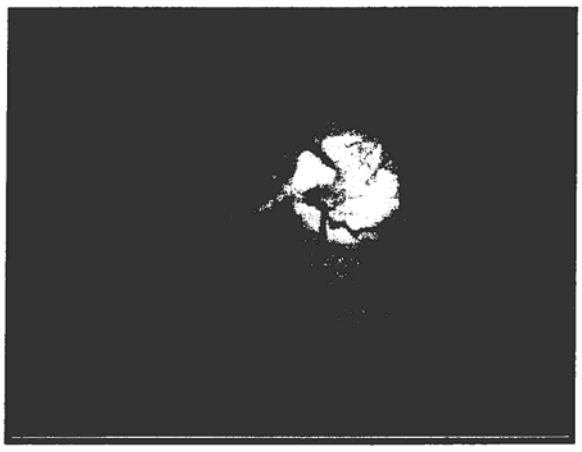

Fig. 6a. Colour photograph of the optic disc with neovascularization

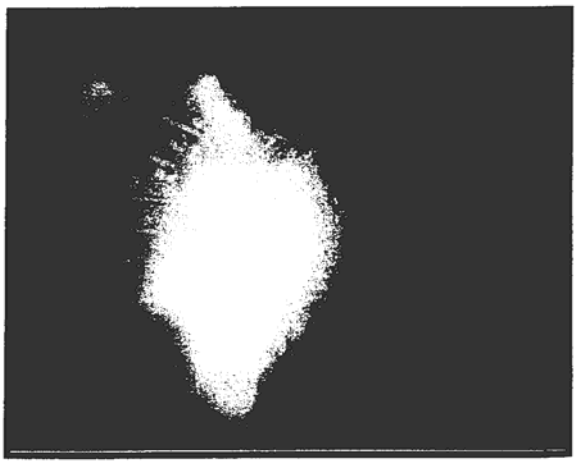

Fig. 6b. Late frame of fundus fluorescein angiography showing extensive dye leakage at the optic disc from new vessels.

The patient merely presents with loss of vision. The clinical picture varies according to the extent of damage of optic nerve, the signs include white or dirty grey, slightly raised disc with poorly delineated margins caused due to gliosis and decrease in number of small blood vessels.[79] The prognosis is very poor as there is no treatment to redeem vision. Hence, utmost care should be taken to prevent any damage to the other 'seeing eye'.

RETINAL COMPLICATIONS

The most distressing effects of diabetes on the eye with regard to visual prognosis are on the retina. The retinal vascular system appears to be the prime target. Retinal complications due to diabetes include diabetic retinopathy, the most severe of the several ocular complications of diabetes, lipaemia retinalis and retinal vein occlusion.

Diabetic retinopathy

Diabetic retinopathy (DR) is a common complication of diabetes posing a serious threat to vision, and is seen in both type 1 and type 2 diabetes. The clinical hallmarks of DR include capillary dilatation, microaneurysms, increased vascular permeability leading to edema, and endothelial cell proliferation. This condition may occur with or without the other systemic complications of diabetes and its incidence increases with duration of diabetes.

Classification and Prevalence

Classically, retinopathy has been graded as nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR). Progression from mild, to moderate, and then to severe, NPDR indicates progressive ischemia in the retina and an increased risk for the development of PDR[82] characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. Proliferative diabetic retinopathy (PDR) is an advanced and severe form of retinopathy. Figure 6 (a and b) shows the Colour and Fundus Fluorescein Angiography photographs of a male diabetic patient aged 57 yrs with extensive neovascularization at the optic disc.

In the Indian scenario the prevalence of DR is lower compared to most other populations. The prevalence of DR in a clinic cohort of 6792 type 2 diabetic patients was 34.1% which included 30.8% with NPDR, 3.4% with PDR and 6.4% had diabetic macular edema.[83] DR may be present even at the time of diagnosis due the insidious onset of type 2 diabetes. In a study of consecutive 500 newly diagnosed type 2 diabetic patients, it was observed that 7.3% already had diabetic retinopathy at the time of diagnosis of diabetes[84], whereas in the UKPDS[85] the prevalence of diabetic retinopathy at the time of diagnosis of diabetes was 35%. In a recently conducted CURES (Chennai Urban Rural Epidemiology Study) Eye study; the first population-based study, which used four-field stereo retinal photographs and ETDRS grading to document DR in the Indian population, the overall prevalence of DR in urban population was 17.6%. Among the known diabetic subjects, 20.8% had DR while it was there in 5.1% of newly detected diabetic subjects.[4]

In another population based study in Chennai, the Chennai Urban Population Study (CUPS), which included both known and newly detected diabetic individuals among the middle and lower socioeconomic groups, 17.5% had non-proliferative diabetic retinopathy while 1.5% had proliferative diabetic retinopathy.[86]

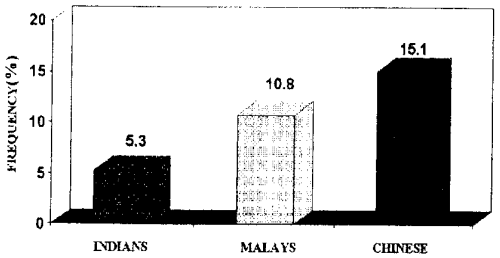

Fig. 7. Prevalence of retinopathy in the Asian Young Diabetes Study (ASDIAB) (Ref 87)

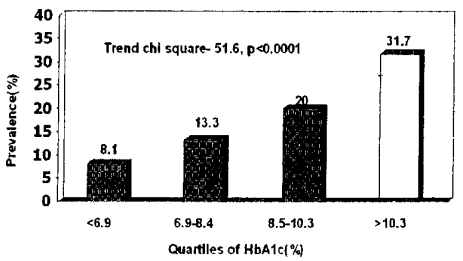

Fig. 8. Prevalence of retinopathy in quartiles of HBAIC levels-the Chennai Urban Rural Epidemiology Study (Ref. 4)

In a study done in young diabetics in Asia called as ASDIAB, the prevalence of DR was least among Indians (5.3%) as compared to other ethnic groups like Malays (10%) and Chinese (15.1%) (Figure 7).[87] Higher levels of fasting C-peptide and glucagon stimulated C-peptide among the Indians in this study, may partly explain the lowest prevalence of DR in this group.

Risk Factors

The onset and progression of DR may be influenced by many systemic factors and ocular factors (Table 2). In a large clinic based study conducted in Chennai, it was shown that NPDR and PDR increased with increasing duration of diabetes. In this study, in type 2 diabetic subjects of 20 years or longer duration, 73% had NPDR and 11.9% had PDR.[83] In the CURES Eye study severity of retinopathy proportionally increased with length of duration of diabetes and it has been observed that for every five year increase in duration of diabetes, the risk for DR increased by 1.89 times.[4] In Joslin clinic patients, there appears to be excess females over males in the older-onset group, however, among those with PDR, males equal females in number[88] while in the clinic cohort in Chennai, DR appeared to be more prevalent in the males compared to females at a ratio of 2:1.[83]

Recent data from epidemiological studies and clinical trials have shown that hyperglycemia is associated with increased incidence and progression of diabetic retinopathy in both type 1 and 2 diabetes.[5-7] Hyperglycemia, as measured by glycated hemoglobin levels, is a significant risk factor for the progression of diabetic retinopathy.[89] It has been shown in the CURES Eye study[4] that there was a linear trend in the prevalence of retinopathy with increase in quartiles of HBA_{1c} [trend chi square: 51.6, $p<0.001$] as shown in Figure 8.

Hypertension an established risk factor for retinopathy has been hypothesized, to damage the retinal capillary endothelial cells by increase in sheer stress of the blood flow. In CURES Eye study, conducted on 26,001 individuals in Chennai, among diabetic subjects with hypertension the prevalence of DR was higher [18.8 %] but this did not reach statistical significance.[4] In the UKPDS, hypertensive patients with type 2 diabetes assigned to tight control had a 34% reduction in progression of retinopathy.[90]

Dyslipidemia, independent of glycemia, has also been shown to be associated with an increased risk of developing retinopathy in the WESDR and Early Treatment Diabetic Retinopathy Study (ETDRS), although the results have not been consistent.[91] An association of diabetic macular edema in type 2 diabetic subjects with increased LDL levels has been shown in earlier study by Rema et al.[92] It has also been shown that in type 2 diabetic subjects there is an increase in the lipid peroxidation in erythrocyte cell membrane and plasma and this is accentuated in patients with diabetic complications.[93] An association of DR has been observed with total cholesterol and serum triglycerides even after adjusting for age, as age by itself is a significant risk factor for hyperlipidemia in the CURES eye study. Diabetic Macular Edema also showed a strong correlation with high LDL levels in the study.[94] The role of oxidant stress in the causation of DR is being increasingly recognized.[95,96]

Microalbuminuria has been associated with the presence of retinopathy in persons with diabetes and may be a marker for the risk of developing proliferative retinopathy.[97] In the CURES Eye Study proteinuria was present in 29.2% of the subjects with DR.[4] Other studies have shown a varying prevalence of DR from 75% to 86% in diabetic subjects with nephropathy.[98]

Local factors such as uveitis and cataract extraction may also accelerate the progression of DR.[99] In a retrospective analysis of type 2 diabetic subjects who underwent cataract surgery, Rema et al have reported that 44% had progression of DR after cataract surgery and this was mainly in patients who underwent extra capsular cataract extraction with IOL implantation.[59]

Recent studies have provided evidence that control of hyperglycemia is important to prevent diabetic retinopathy, however, some patients develop DR despite good control and others escape retinopathy despite poor control. This suggests the role of genetic factors in susceptibility to retinopathy.[100] Various studies have shown an association of genetic factors with retinopathy.[101-103] In a study conducted in 322 Type 2 diabetic families, Rema et al reported that there was a familial clustering of diabetic retinopathy among siblings of diabetic probands with and without DR. The odds ratio was 3.5 suggesting that siblings of the probands with DR had 3.5 times higher risk of developing retinopathy.[104] Recently a study done on 249 Mexican-American type 2 diabetic siblings of probands with DR showed that the severity of DR aggregates in families rather than the incidence of DR itself.[105]

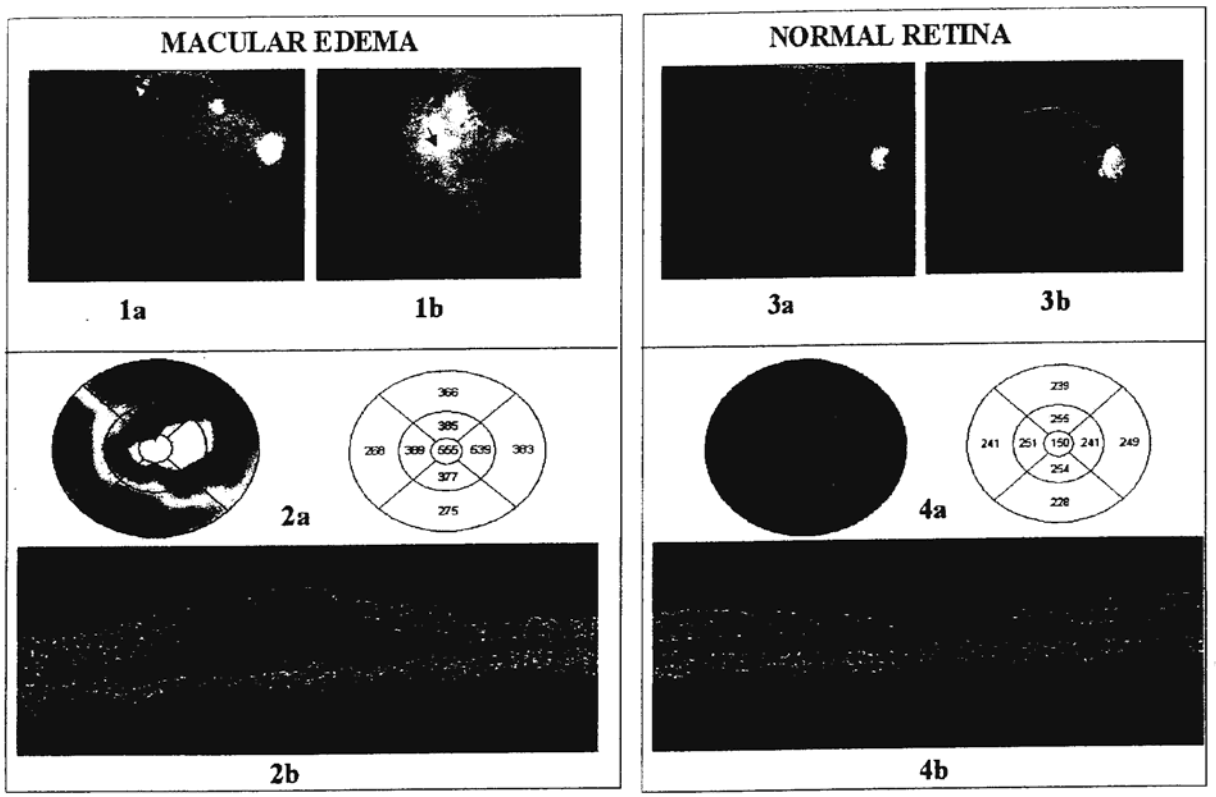

Fig. 9. Comparison of OCT images in Macular Edema and normal retina.

1a. Colour photography of the right eye of a male diabetic subject shows exudates in the macular region. An area of retinal thickening can be seen within the exudative ring.
1b. Fundus Fluorescein Angiography (FFA) of the same eye shows diffuse dye leak all around the fovea as indicated by black arrows.
2a. The colour thickness map shows evidence of fluid collection as indicated by the red colour and the thickness of foveal region is 555m
2b. A single OCT image through the foveal region of the same patient shows disruption of foveal contour. Increased retinal thickness and extensive fluid accumulation is observed in the neuro sensory retina.
3a. Colour picture of the right eye of a normal individual shown for comparison.
3b. FFA picture outlines a normal fovea and peri-foveal network.
4a. The colour reflection map shows a normal foveal depression and colour within normal range.
4b. A single OCT line scan of the macula region shows normal foveal contour. The foveal thickness is 150 m.

Screening of DR

As individuals with sight- threatening retinopathy may not have symptoms, life-long evaluation for retinopathy by retinal screening of diabetic individuals is a valuable and necessary strategy.[106] To prevent diabetes related visual impairment, the treatment must be appropriately timed and rigorous.[107] Table 3 outlines the recommended diabetic eye examination schedule.

Sight-threatening diabetic retinal disease (STDRD) can be effectively identified using the direct ophthalmoscopy, Indirect ophthalmoscopy coupled with biomicroscopy with 70D lens and seven-standard field stereoscopic 30° fundus photography (gold standard). However, digital colour photography has now replaced this cumbersome mode of screening. Non mydriatic cameras are effective for screening at physicians' office but not sensitive enough to pick up changes like microaneurysms and subtle neovascularisation.

Recently several new, noninvasive techniques promise to improve diagnostic sensitivity, one such technique is the Optical Coherence Tomography (OCT). This method correlates well with Fundus Fluorescein Angiography (FFA). This noninvasive technique helps to study the cross sectional anatomy

of the retina, to obtain high resolution cross-sectional images of the macula and for evaluation and follow up of patients with diabetic macular edema. OCT provides objective and quantitative measurements that are not possible with other techniques. Figure 9 depicts an OCT image in an individual with macular odema. Other newer diagnostic techniques include Retinal Thickness Analyser, GDx VCC digi scope, etc., which need further refinement.

Surgical interventions include laser photocoagulation therapy and vitreoretinal surgery. Two large randomized, controlled clinical trials demonstrated that laser photocoagulation therapy decreases visual disability due to DR by 90% if instituted at the correct stages.[108-110] In a clinic-based study conducted in 261 eyes of 168 Type 2 diabetic subjects who underwent Pan Retinal Photocoagulation (PRP) at Chennai, 73% eyes maintained ≥ 6/9 at 1-year follow-up. Visual acuity at baseline and duration of diabetes played a significant role in determining the post PRP visual acuity.[111] Vitreous surgery may allow visual rehabilitation in many eyes that are otherwise untreatable.

Further details on Diabetes Retinopathy (DR) are dealt with in the next chapter.

Lipemia retinalis

One of the rare ophthalmological complications of hypertriglyceridemia is lipemia retinalis, which may be seen in unregulated diabetic individuals with diabetic coma. The retinal picture shows retinal vessels with "milky" chylomicron-rich plasma. The retinal vessels may be distended afftecting the blood flow. Davies in 1955[112] has reported that roughly 5/6 of cases of lipemia retinalis occur in diabetic subjects. This condition develops when serum triglyceride levels exceed 2.5 g/100 ml, more likely in levels between 3 and 3.5 g/100 ml. Even though lipemia retinalis does not cause significant visual loss, a recent study has demonstrated that it may be associated with vascular pathology, such as a branch retinal vein occlusion with marked exudative response and decreased visual acuity.[113] Reversal of this condition can be achieved by lowering triglycerides levels or by controlling ketosis without a sequel.

Retinal vein occlusion

Retinal vein occlusion (RVO) is one of the common retinal vascular diseases responsible for visual disability.[114] Visual loss can vary from mild or severe and the two complications related with a poor visual outcome include macular oedema and severe retinal ischaemia. Although RVO is not a complication of diabetes per se, this condition is said to occur more frequently in diabetic individuals compared to non diabetic individuals. RVO is classified into Branch RVO, Central RVO and Hemi RVO. Arteriolosclerosis is an important contributing factor for BRVO and the other factors associated with increased risk for RVO include advancing age, systemic disorders (diabetes, hypertension, hyperlipidemia) and increased intraocular pressure. In a clinic based study conducted in Chennai, the overall prevalence of RVO was 0.6% in type 2 diabetic subjects. This study also showed that diabetic retinopathy was found to be significantly higher in the subjects with RVO (73.5%) compared to those without RVO (27.4%)[115] in patients with type 2 diabetes.

SUMMARY

- As ocular complications in diabetes represents an end organ response to a generalized metabolic abnormality affecting all structures of the eye, routine, repetitive, lifelong, expert clinical examination after dilatation is essential for the fundamental ophthalmic care of the patient with diabetes.
- The most serious threat to vision are Diabetic Macular Edema and Proliferative retinopathy, which are treatable by laser, thus identification and timely treatment of these two conditions are mandatory to preserve vision.
- In diabetic individuals especially type 2 diabetes mellitus, open angle glaucoma is two times more frequent than normal individuals, hence evaluation for glaucoma by Optical Coherence Tomography (OCT) and field testing is essential
- Optimal ophthalmic care for diabetic individuals must include diligent evaluation and treatment of concomitant systemic disorders like hypertension, nephropathy that influence the development, progression and ultimate outcome of ocular manifestations.
- Optimization of these systemic considerations through an intensive, multi-disciplinary, healthcare team-based approach will maximize the ophthalmic and general health of these individuals.

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