The eye in diabetes

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INTRODUCTION

Diabetes mellitus (DM) affects more than 100 million people worldwide. In Western countries the prevalence is between 2 and 4% of the population while in Asia the incidence is increasing (King et al, 1998). Population studies all over the world show that the prevalence of type 2 DM is escalating and is likely to reach epidemic proportions. In 1985, the estimated population of diabetic individuals in the world was 30 million but by 1995 it had increased to 135 million. Based on current trends, epidemiologists predict that the population of diabetic individuals will increase to 300 million by 2025.

DM affects almost every part of the eye and is the single most important cause of preventable blindness. The most severe manifestation is diabetic retinopathy (DR), which is the leading cause of visual disability in working-age adults. It is uncommon in the developing world, but as standards of living and life expectancy improve, DM and consequently DR will become a leading cause of blindness as it has been estimated that blindness is 25 times more common in diabetics. Visual impairment occurs as a result of macular oedema, proliferative retinal disease, non-resolving vitreous haemorrhage or traction retinal detachment.

Since DR is often asymptomatic in its most treatable stages, its early detection through regularly scheduled ocular examinations (screening) is critical. Although much is known about diabetic eye disease, many patients still present very late with irreversible visual loss. Increasing patients' awareness of the effect of DM on the eye will help reduce ocular morbidity. Until modalities are in place to prevent or cure DR, the emphasis must be on identification, careful follow up, and timely and adequate laser photocoagulation or surgery, or both, in patients with DR.

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Many landmark clinical trials have been conducted on diabetic eye disease. The Diabetic Control and Complications Trial (DCCT) Research Group (1995) has reported that good control of DM reduces the incidence of severe eye disease. The trial showed that if blood sugar is maintained near normal levels over a long period of time the risk of DR is reduced by 76%. It was also shown in this trial that the level of glycosylated haemoglobin could be used to predict the incidence and progression of DR. However, this is not an indication for intensive insulin therapy for all patients with type 2 diabetes. There is also evidence that too rapid an improvement of chronic poor control may increase the risk of short-term DR progression. This article reviews the epidemiology, pathogenesis, clinical features, treatment options and screening for diabetic eye disease.

EPIDEMIOLOGY OF DR

For both type 1 and type 2 DM, the best predictor of DR is the duration of systemic disease. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) conducted the most comprehensive epidemiological study. Comparing type 1 with type 2 DM, the highest incidence of new DR was found in type 1 diabetics (*Table 1*). Type 1 diabetic patients demonstrate the strongest relationship between DR and duration of disease. As many as 60% of type 1 diabetics without DR at the start of the study developed it over a 4-year period. Significant progression of DR to proliferative disease also occurred in one in ten patients with non-proliferative disease within 4 years (Klein et al, 1989b).

On the contrary, in type 2 DM patients DR is often present at the time DM is diagnosed, particularly macular oedema, and the frequency of DR never reaches the high prevalence of type 1 disease even after 25 years. Risk factors for DR have also been identified in the WESDR (Klein et al, 1989a). It is hoped that manipulation of these factors at the onset of DR may delay or prevent DR.

FACTORS INFLUENCING DEVELOPMENT OF DR

1. Genetic risk factors are important in both types of DM. In type 1 DM, HLA-B51 increases the risk of developing DR. Identical twin studies in type 2 DM have shown similar grades of DR in sibling pairs more often than can be related to chance alone.
2. Data from WESDR and the United Kingdom Prospective Diabetes Mellitus Study (UKPDS) (2001)

TABLE 1.
Comparison of type 1 and type 2 diabetes mellitus

Risk factors	Type 1	Type 2
Genetic factors	HLA-B51	None
Control of blood sugar	Important role	Important role
Insulin use	Worse DR	Worse DR
Age	DR is rare before puberty (Krolewski et al, 1986). Older age is related to severity of DR and macular oedema and is a recognized risk factor for severity of DR (Moss et al, 1998)	Older age is related to macular oedema
Hypertension	Important risk factor for ischaemic maculopathy	Tight control is useful
High lipid level	Associated with more retinal exudates (Chew et al, 1996) and progression of DR (Dornan et al, 1982)	

DR = diabetic retinopathy

indicate that the incidence of DR is higher if blood sugar is poorly controlled, and progression of DR is also more common in those with worse control. However, once DR is well established, better control of blood sugar does not appear to slow progression of the disease (DCCT, 1993). Therefore it is important that near normoglycaemia is established and maintained from diagnosis to prevent blindness.

3. Insulin use also influences the outcome of DR. The WESDR study found that more diabetic patients using insulin developed DR compared to those controlled by other means (Klein et al, 1992). This could also mean that those on insulin have worse control of their diabetes, hence the worse DR.

Diabetes, hypertension, dyslipidaemia and obesity commonly co-exist in the same patient. These factors, together with cigarette smoking, positive family history and the presence of proteinuria, are major risk factors for macrovascular disease. High alcohol consumption is associated with a three-fold increased risk of more severe retinal disease (Moss et al, 1994). Renal disease is known to be associated with the development and progression of DR. Hormonal factors such as puberty and pregnancy (Sunness, 1988) can also result in progression of DR.

PATHOGENESIS OF DR

DR is a form of microangiopathy which affects the retinal precapillary arterioles, capillaries and venules. The basic pathogenesis is microvascular occlusion and leakage. At the level of capillaries, there is pericyte drop out, thickening of the basement membrane, endothelial cell damage and proliferation. Red blood cells are deformed, which leads to decreased oxygen transport. Changes in platelets also lead to increased stickiness and aggregation.

All these changes lead to retinal capillary occlusion and non-perfusion, which in turn causes retinal hypoxia later leading to formation of arteriovenous shunts, often referred to as intraretinal microvascular abnormalities (IRMA), and neovascularization. The stimulus for neovascularization on the retina, optic nerve head and iris is thought to be vasoendothelial growth factor, a vasoformative substance released by hypoxic retinal tissue.

The pathogenesis of microvascular leakage is related to hyperglycaemia causing apoptosis of retinal capillary pericytes and retinal capillary endothelial cells. These changes lead to increased vascular permeability and a breakdown of the retinal barrier which in turn causes intraretinal haemorrhage, oedema and exudates which are composed of lipoprotein and lipid-filled macrophages. Microangiopathy is also clinically apparent in the kidneys and vasa nervorum of peripheral nerves as well as the eyes.

RETINAL FEATURES OF DR

There is a typical evolution of retinal features in DR, which require different treatment regimens to prevent or treat visual loss. Background DR consists of microaneurysms and small round haemorrhages (dots and blots) (*Figure 1*). Patients with mild or moderate non-proliferative DR generally are not candidates for scatter (panretinal) laser surgery and can be followed safely at 6–12-month intervals as determined by the examiner.

Preproliferative DR is defined by the presence of multiple cotton wool spots, large blot haemorrhages (*Figure 2*), IRMAs (*Figure 3*), venous beading, and regions of retinal non-perfusion/ischaemia (*Figure 4*). If patients are reliable preproliferative DR can usually be monitored every 4–6 months until higher-risk characteristics develop. However, it may be appropriate to treat one eye if the patient is unreliable in returning for review. In addition the treatment of other systemic factors, such as blood pressure, lipid level and blood sugar level, is crucial to prevent progression.

Proliferative DR is characterized by neovascularization at the disc (NVD) or elsewhere in the fundus (NVE) (*Figure 5*). High-risk characteristics for profound visual loss include NVD greater than one quarter of the disc area and vitreous or preretinal haemorrhage associated with NVD or NVE (*Figure 6*). When such criteria are present, urgent laser treatment is recommended.

Figure 1. Background diabetic retinopathy showing microaneurysms, small round haemorrhages (blots and dots) in the macula.

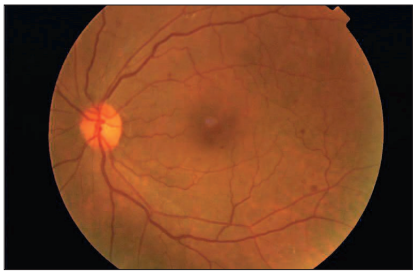


Figure 2. Preproliferative diabetic retinopathy showing presence of cotton wool spots and large blot haemorrhages.

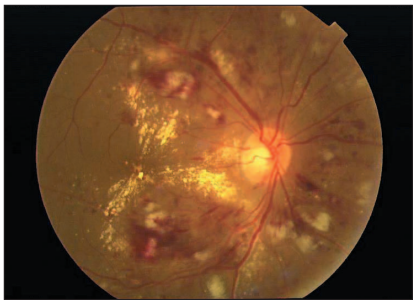


Figure 3. Preproliferative diabetic retinopathy showing intraretinal microvascular abnormalities.

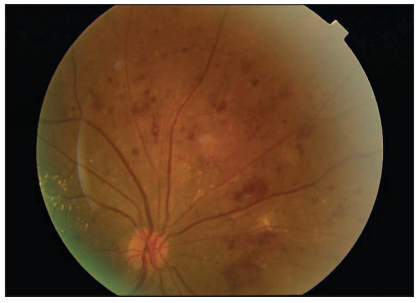
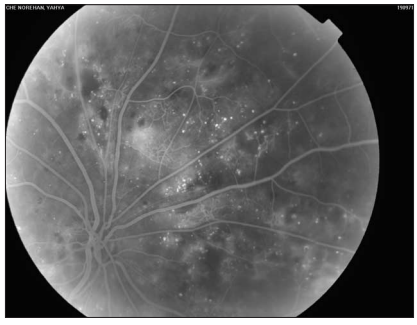


Figure 4. Fundus fluorescein angiography showing regions of retinal non-perfusion/ischaemia.



Advanced DR is characterized by vitreous haemorrhage (*Figure 7*), tractional retinal detachment (*Figure 8*), opaque or ochre membrane of posterior hyaloid face, synchysis scintillans and lipaemia retinalis.

The Diabetic Retinopathy Vitrectomy Study (DRVS) demonstrated that early vitrectomy was better than vitrectomy after 1 year of vitreous haemorrhage in juvenile-onset diabetes (DRVS, 1990). This benefit was not found in adult-onset diabetic vitreous haemorrhage, which can be observed and will probably clear spontaneously. However, if the vitreous haemorrhage is dense, relatively immobile, and yellow-ochre in colour or is associated with multiple vitreoretinal traction points, vitrectomy may be needed earlier.

Figure 5. Proliferative diabetic retinopathy showing retinal neovascularization at the optic disc and elsewhere.

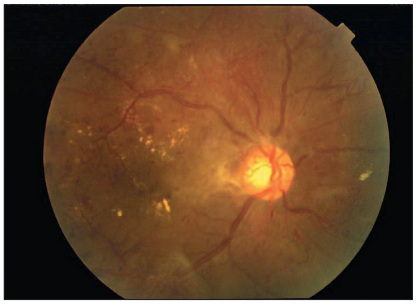


Figure 6. High-risk characteristics for profound visual loss, i.e. neovascularization of the optic disc and retina with preretinal haemorrhage.

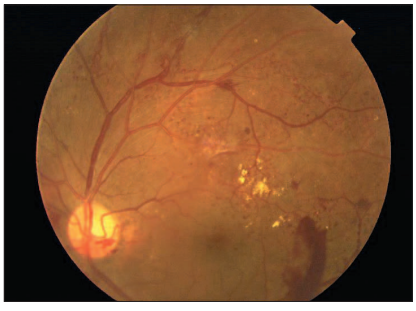
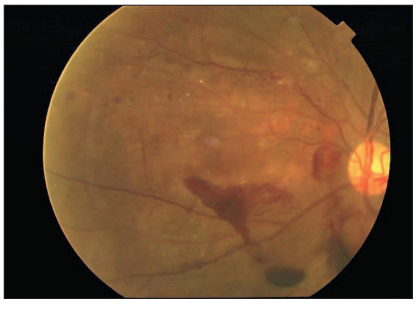


Figure 7. Advanced diabetic retinopathy showing vitreous haemorrhage.



MACULAR INVOLVEMENT IN DIABETIC RETINOPATHY

Diabetic maculopathy is the commonest cause of visual impairment, especially near vision which is impaired in diabetics. Diabetic macular oedema may be present at any stage of DR and alters the structure of the macula affecting its function. Effects of DM on the macula include macular oedema (collection of intraretinal fluid in the macula with or without lipid exudates) (*Figure 9*), non-perfusion of capillaries of the macula, traction in the macula by fibrous tissue proliferation and intraretinal or preretinal haemorrhage in the macula.

The presence of macular oedema, even with mild or moderate degrees of non-proliferative diabetic retinopathy, requires follow up in a shorter period and can be treated by focal direct laser to focal leaks and grid laser treatment to diffuse leakage or thickened avascular zones. In the Early Treatment Diabetic Retinopathy Study (ETDRS) eyes with macular oedema benefited from focal argon laser photocoagulation treatment when compared to untreated eyes in a control group (ETDRS, 1985). Treatment for macular oedema reduced the risk of moderate visual loss, increased the chance of visual improvement, and was associated with only minor losses of visual field.

Figure 8. Advanced diabetic retinopathy showing tractional retinal detachment affecting the macula.

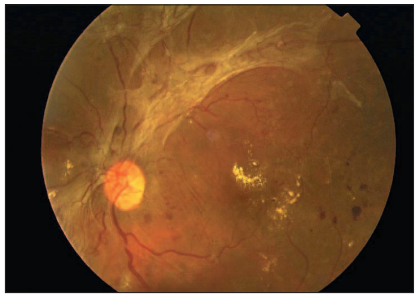
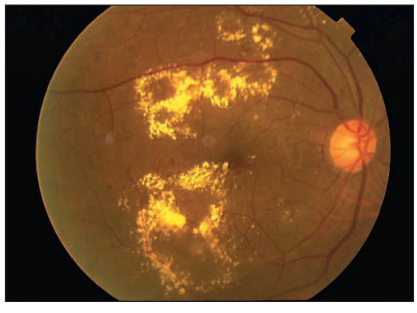


Figure 9. Diabetic exudative maculopathy showing collection of intraretinal lipid also called hard exudates.



NON-RETINAL DIABETIC OCULAR DISEASE

Cataract is the most common non-retinal finding in DM. Significant cataract was found in 60% of diabetics aged between 30 and 45 years in the WESDR (Davis et al, 1985), a five-fold increase in prevalence over that in a control population. This is thought to be linked to abnormal levels of antioxidants and to be an acceleration of age-related cataract. Cataract surgery in diabetics is often more complicated because of poor iris dilatation and a higher incidence of postoperative inflammation. It is also associated with worsening of maculopathy and proliferative DR, and for this reason laser treatment is used to stabilize DR before cataract surgery.

Glaucoma is also more common in DM although the mechanism of this is not clear. Abnormal deposition of glycoprotein in the iris in DM may affect pupil size and shape and alter aqueous drainage channels, as may diabetic neuropathy affecting the autonomic nervous system of the iris. Retinal circulation in diabetic individuals may be compromised, and thus may make glaucomatous optic disc damage more likely.

Cranial nerve palsies may occur in diabetics and is thought to be caused by microvascular disease, which affects small vessels supplying the motor cranial nerves. The sixth cranial nerve is most commonly affected and third nerve palsy is also well recognized and is characteristically pupil sparing. The majority of cases recover.

Retinal vascular disease is commoner in DM because of the atherogenic effect of diabetes. Increased rigidity and thickness of retinal arterial walls is also caused by hypertension, usually associated with DM causing impaired

venous return where an artery crosses a vein, resulting in retinal vein occlusion. Involvement of the arterial supply to the optic nerve results in ischaemic optic neuropathy. Asteroid hyalitis in which there are cholesterol crystals in the vitreous can cause difficulty visualizing the fundus but does not cause difficulties for the patient seeing out.

SCREENING

The aim of screening is to select those who are at higher risk of developing a disease and to offer intervention to prevent progression. Screening should be vigorously carried out if DR is to be effectively treated and ocular morbidity prevented (Ackerman, 1992). Direct ophthalmoscopy is the easiest and most widely available technique. However, the sensitivity and specificity of the technique has been poor. The most successful methods are photographic schemes on 35 mm film or digital imaging-based biomicroscopy performed by trained optometrists or doctors.

The most cost-effective timing remains controversial, but it is generally accepted that type 2 diabetics should be examined at the onset of their disease, then yearly thereafter. Type 1 diabetics do not have to be examined until 5 years into their disease course, and no sooner than puberty. If DR is detected, the frequency of examinations should be set accordingly. If there is no background DR in diabetic patients, fundus photographs are taken for future comparison and the patient screened again at 1–2-year intervals.

Screening frequency should be increased if there are high-risk associations such as pregnancy, renal failure or poorly controlled hypertension.

CONCLUSION

DM is a metabolic disorder associated with serious ocular complications. The incidence (Amos et al, 1997) of DM continues to rise and a major epidemic is predicted. The management of such preventable disease is rewarding. With due care and attention to risk factors for diabetic complications, a significant proportion of diabetes-associated visual disability can be avoided. At present prevention, detection, management and understanding of DR pose continuing challenges for both patients and health-care professionals. Diabetic patients deserve best efforts by health-care professionals to improve their lifestyle. HM

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