Indian J Med Res 125, March 2007, pp 297-310

Diabetic retinopathy: An Indian perspective

M. Rema & R. Pradeepa

Madras Diabetes Research Foundation & Dr Mohan's Diabetes Specialities Centre, Chennai, India

Received November 8, 2006

Diabetic retinopathy (DR) can be defined as damage to microvascular system in the retina due to prolonged hyperglycaemia. The prevalence of DR in the Chennai Urban Rural Epidemiology (CURES) Eye Study in south India was 17.6 per cent, significantly lower than age-matched western counterparts. However, due to the large number of diabetic subjects, DR is likely to pose a public health burden in India. CURES Eye study showed that the major systemic risk factors for onset and progression of DR are duration of diabetes, degree of glycaemic control and hyperlipidaemia. Hypertension did not play a major role in this cross-sectional analysis. The role of oxidative stress, atherosclerotic end points and genetic factors in susceptibility to DR has been studied. It was found that DR was associated with increased intima-media thickness and arterial stiffness in type 2 Indian diabetic subjects suggesting that common pathogenic mechanisms might predispose to diabetic microangiopathy. Curcumin, an active ingredient of turmeric, has been shown to inhibit proliferation of retinal endothelial cells *in vivo*. Visual disability from DR is largely preventable if managed with timely intervention by laser. It has been clearly demonstrated that in type 2 south Indian diabetic patients with proliferative DR who underwent Pan retinal photocoagulation, 73 per cent eyes with good visual acuity (6/9) at baseline maintained the same vision at 1 yr follow up. There is evidence that DR begins to develop years before the clinical diagnosis of type 2 diabetes. Our earlier study demonstrated that DR is present in 7 per cent of newly diagnosed subjects, hence routine retinal screening for DR even at the time of diagnosis of type 2 diabetes may help in optimized laser therapy. Annual retinal examination and early detection of DR can considerably reduce the risk of visual loss in diabetic individuals.

Key words Diabetic retinopathy - Indian subjects - prevalence - risk factors - type 2 diabetes mellitus

Diabetic retinopathy (DR) is a vascular disorder affecting the microvasculature of the retina. It is estimated that diabetes mellitus affects 4 per cent of the world's population, almost half of whom have some degree of DR at any given time[1]. DR occurs both in type 1 and type 2 diabetes mellitus and has been shown that nearly all type 1 and 75 per cent of type 2 diabetes will develop DR after 15 yr duration of diabetes as shown in earlier epidemiological studies[2,3]. In the western population, DR has been

shown to be the cause of visual impairment in 86 per cent of type 1 diabetic patients and in 33 per cent of type 2 diabetic patients[4].

In India with the epidemic increase in type 2 diabetes mellitus as reported by the World Health Organization (WHO)[5], diabetic retinopathy is fast becoming an important cause of visual disability. Visual disability from diabetes is a significant public health problem; however this morbidity is largely preventable and treatable. If managed with timely intervention, the quality of life can be preserved. This review aims at providing an overview of diabetic retinopathy in the Indian scenario.

Classification and prevalence of diabetic retinopathy

Diabetic retinopathy is primarily classified into non proliferative DR (NPDR), formerly termed simple, or background retinopathy, and proliferative DR (PDR). Progression from mild, characterized by increased vascular permeability, to moderate, and then to severe NPDR characterized by vascular closure and an increased risk for the development of PDR[2] distinguished by the growth of new blood vessels on the retina and posterior surface of the vitreous. Visual impairment in diabetic retinopathy occurs due to diabetic macular edema (DME) and PDR. DME is defined as retinal thickening/hard exudates within 500 μ of the centre of the macula which is due to increased permeability of retinal vessels leading to macular oedema and retinal thickening. The other cause of visual impairment in DR is PDR where there may be a sudden vitreous haemorrhage from the unstable new vessels resulting in total or partial visual loss or from pre-retinal haemorrhage/fibrosis or traction at the macula.

The prevalence of DR varies in type 1 and type 2 diabetes. In type 1 diabetes in the EURODIAB IDDM complications study, which included subjects attending 31 European diabetes centres, the prevalence of DR ranged between 25-60 per cent[6]. In India, there is a paucity of data on the prevalence of DR in type 1 diabetes mellitus, as a registry for prevalence of type 1 diabetes is only recently being set up in the country. An earlier study done in a clinic-based population reported an overall prevalence of 14 per cent. NPDR was observed in 6 per cent, while 4 per cent had macular oedema and 4 per cent had PDR[7]. Asian Young Diabetes Research (ASDIAB) Study, reported the prevalence of DR in 724 young diabetic subjects of age 12-40 yr with duration of diabetes < 12 months in 7 centres of four Asian countries. It is interesting to note that DR prevalence was least among Indians (5.3%) as compared to other ethnic groups like Malays (10%) and Chinese (15.1%)[8]. Higher levels of fasting C-peptide and glucagon stimulated C-peptide among the Indians in this study, may partly explain the lower prevalence of DR in this group.

In a clinic population of a cohort of 6792 type 2 diabetic patients attending a diabetes centre at Chennai in south India the prevalence of DR was 34.1 per cent. The retinal screening was done by a combination of ophthalmoscopy and retinal photographs. The prevalence included 30.8 per cent with NPDR, 3.4 per cent with PDR and 6.4 per cent had DME[9]. However, in the Chennai Urban Rural Epidemiology (CURES) Eye Study, a population based study which included a representative sample of 26,001 individuals (urban component), the overall prevalence of DR was 17.6 per cent among the 1715 diabetic subjects[10]. Among the known diabetic subjects, the overall prevalence of DR was 20.8 per cent, while among the newly detected diabetic subjects 5.1 per cent had DR. Higher frequency of all the grades of retinopathy (overall, NPDR and PDR) was observed in known diabetic subjects compared to newly detected cases (Fig. 1). Prevalence of DME in the total diabetic population was 5.0 per cent while among the known diabetic subjects it was 6.3 and 1.1 per cent among the newly diagnosed diabetic subjects[10]. The CURES Eye study is the first population-based study, which used four-field stereo retinal photographs and Early Treatment Diabetic Retinopathy Study (ETDRS) grading to document DR in the Indian population[11].

Two other population-based studies conducted in south India, reported overall prevalence of DR as 22.4 per cent[12] and 26.8 per cent respectively; however they were not based on retinal photography[13]. The prevalence of DR in different socio-economic groups was studied in the Chennai Urban Population Study (CUPS), a population based study conducted in Chennai, involving two residential areas representing the lower and middle income group. The prevalence of DR in the middle income group was 21.1 per cent compared to 14.3 per cent in the low income group[14]. It is noteworthy that the prevalence of diabetes was higher in the middle income group (12.4%) compared to lower socio-economic strata (6.5%), which is contradictory to the western population studies where diabetes is reported to be higher among the lower economic strata[15].

Lack of symptoms and the insidious onset of type 2 diabetes may result in development of DR at an early stage[16]. Often DR is detected when type 2 diabetes is diagnosed. Rema *et al*[17] in a study of 438 consecutive newly diagnosed type 2 diabetic patients reported that 7.3 per cent already had diabetic retinopathy. However, in the population based CURES Eye study the prevalence of DR at onset of type 2 diabetes was 6.7 per cent lower as expected when a population based study is done[18]. These figures are strikingly lower than those reported in Europeans, where the prevalence of retinopathy at diagnosis was reported to vary from 28 to 35 per cent[3,19]. In studies conducted in USA and Australia, the prevalence of retinopathy at the time of diagnosis of type 2 diabetes varied from 10-21 per cent[20-22].

The propensity to develop DR is lower in south India compared to the other populations. Table I provides the prevalence of DR in different populations varying from 17.6 per cent in Chennai, India, to 50.3 per cent in Wisconsin, US[10,23-29]. It has been hypothesized that this may be due to the fact that Indians develop type 2 diabetes at an earlier age, but on matching for age the prevalence was still significantly lower than their western counterparts (19.2%). Inherent ethnic difference in the Indians in relation to the susceptibility to DR may be one aspect and another reason may be the type of diet which although rich in carbohydrates includes more vegetables, less fat and perhaps more antioxidants and anti-inflammatory agents like curcumin.

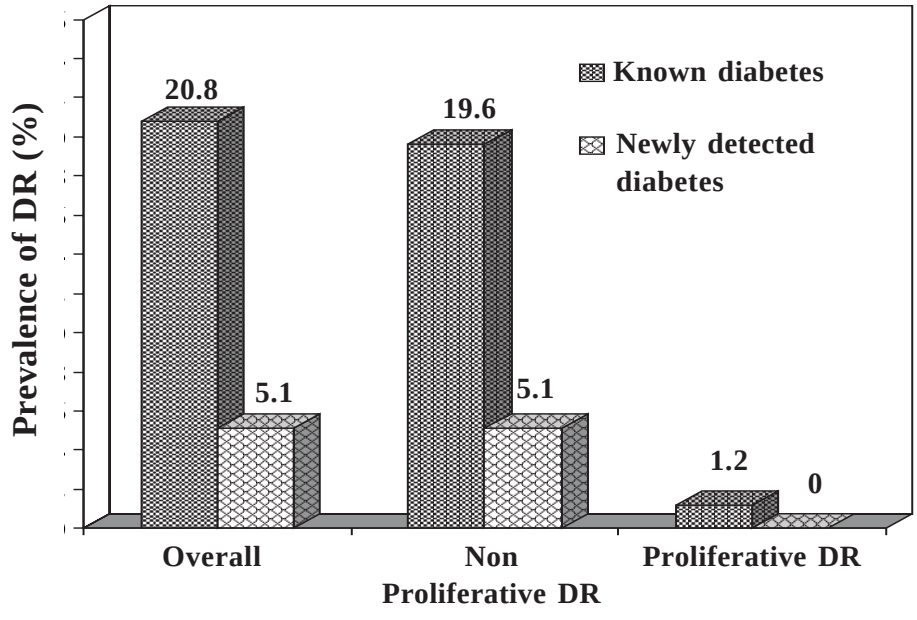

Fig. 1. Prevalence of retinopathy - the Chennai Urban Rural Epidemiology Study. *Source*: Ref. 10.

Molecular basis of diabetic retinopathy

The retinal changes in patients with diabetes result from five fundamental processes: (*i*) the formation of retinal capillary microaneurysms, (*ii*) the development of excessive vascular permeability, (*iii*) vascular occlusion, (*iv*) the proliferation of new blood vessels and accompanying fibrous tissue on the surface of the retina and optic disk, and (*v*) the contraction of these fibrovascular proliferations and the vitreous[30]. The clinicopathological lesions of diabetic retinopathy have been well classified. Although a multitude of pathogenic mechanisms have been proposed, the underlying dysfunctional biochemical and molecular pathways that lead to initiation and progression of DR still remains an enigma.

Currently four major biochemical pathways have been hypothesized to explain the mechanism of diabetic eye diseases all starting initially from hyperglycaemia induced vascular injury[31]. These 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. Studies have suggested that these mechanisms seem to reflect a hyperglycaemia induced process initiated by superoxide overproduction by mitochondrial electron transport chain[32].

Determinants of diabetic retinopathy

Epidemiological surveys have shown that various risk factors known to be associated with diabetic retinopathy, tend to accelerate its course and increase its severity (Table II).

Systemic factors

Gender: Studies have shown varying results when predicting gender as a risk factor for developing DR. In the Joslin clinic patients, there appeared to be excess females over males in the older-onset group, however among those with PDR, males were equal to females[33]. In the clinic cohort in Chennai DR

Table I. Studies on prevalence of diabetic retinopathy in different populations

Populations studied	Place	Year/period	Participants with diabetes (n)	Prevalence of retinopathy (%)
Chennai Urban Rural Epidemiology Study (CURES) - Eye Study-1[10]	Chennai, India	2003 -ongoing	1715	17.6
Los Angeles Latino Eye Study (LALES)[23]	Los Angeles, USA	1999-2003	1217	46.9
The Liverpool Diabetic Eye Study[24]	Liverpool, UK	1998	395	33.6
Barbados Eye Study[25]	Barbados, West Indies	1998	615	28.8
Blue Mountains Eye Study (BMES) [26]	Blue Mountain, Australia	1992-1994	252	29.0
Taiwan[27]	Taiwan, Republic of China	1991	527	35.0
Beaver Dam Eye Study (BDES) [28]	Wisconsin, USA	1988-1990	410	35.1
Wisconsin Epidemiologic Study of Diabetic Retinopathy[29]	Southern Wisconsin, USA	1980-82	1313	50.3

appeared to be prevalent more in the males compared to females (sex ratio 2 : 1)[9]. A similar preponderance has been reported from the CURES Eye study[10], UKPDS study[20] and the Hyderabad study[12].

Duration of disease: The duration of diabetes is probably the strongest predictor for development and progression of retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the widest and most prolonged population based ophthalmologic survey, reported that higher prevalence of DR was associated with longer duration of diabetes[34]. In persons with type 1 diabetes with less than 5 yr of duration, the prevalence of retinopathy was about 10 per cent, whereas it ranged from 25 to 40 per cent in individuals with type 2 diabetes.

In India, virtually all studies have shown an increased prevalence of DR as the duration of diabetes increased[10,12,14]. In the study conducted by Dandona *et al*[12] in type 2 diabetes, it is reported that 87.5 per cent of those with >15 yr duration of diabetes had DR compared with 18.9 per cent of those who had <15 yr duration. In the CURES Eye study[10], 41.8 per cent had DR after 15 yr of diabetes and severity of DR proportionally increased with longer duration of diabetes (Fig. 2). In addition, it has been demonstrated that for every five year increase in duration of diabetes, the risk for DR increased by 1.89 times[10].

Glycaemic control: There is strong evidence to suggest that the development and progression of DR is influenced by the level of hyperglycaemia[10,14,35]. The protective effect of glycaemic control on the development and progression of DR has been investigated in both type 1 (WESDR and Diabetes Control and Complications Trial- DCCT) and type 2 diabetic patients (UKPDS)[35-37]. In the 14 yr progression of retinopathy study (WESDR), the prevalence of retinopathy in type 1 diabetic subjects was 12 per cent when glycated haemoglobin (HbA1c) was <7 per cent as compared to 40.7 per cent when HbA1c levels were >10 per cent and an increased

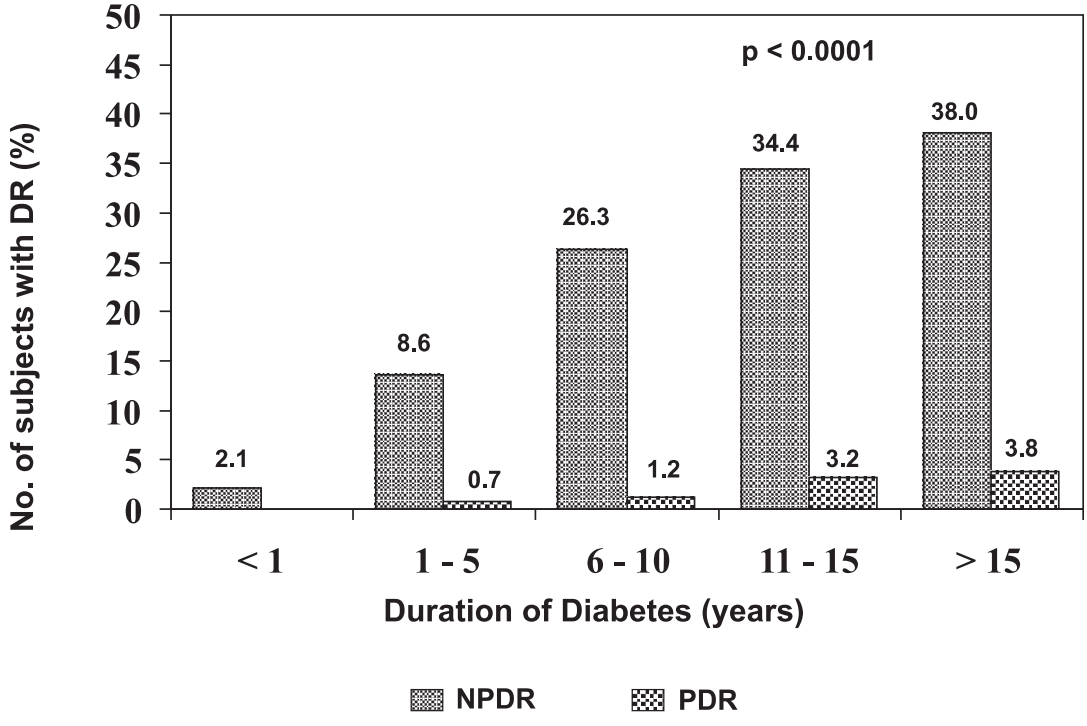

Fig. 2. Severity of retinopathy in relation to duration of diabetes. *Source*: Ref. 10.

risk of PDR was associated with more severe baseline retinopathy and higher HbA1c levels[35]. The DCCT Research Group[36] demonstrated that intensive therapy reduced the mean risk of retinopathy by 76 per cent as compared with conventional therapy in the primary-prevention cohort. While in the secondary-intervention cohort, intensive therapy reduced the risk of eye complications by 54 per cent for the development of DR, decreased progression of NPDR to PDR or severe NPDR by 47 per cent and the need for laser therapy by 56 per cent. Rema *et al*[38] have also shown that the visual outcome of laser photocoagulation for eyes with PDR was also dependent on the degree of glycaemic control.

In the CURES Eye Study, a linear trend in the prevalence of retinopathy with increase in quartiles of HbA1c (trend Chi square: 51.6, $P<0.001$) from 8.1 per cent (HbA1c level < 6.9 %) to 31.7 per cent (HbA1c level >10.3%) was observed. For every 2 per cent elevation of HbA1c, the risk for DR increased by a factor of 1.7[10]. In the UKPDS[37], the risk reduction in eye complications for every 1 per cent decrease in HbA1c was 19 per cent. Thus it is observed that long term glycemic control plays an important role in delaying the onset and lowing down the progression of DR.

Hypertension: Increased blood pressure has been hypothesized, through the effects of increased sheer stress of blood flow, to damage the retinal capillary endothelial cells in eyes of people with diabetes[39]. The possible mechanisms by which hypertension may affect DR are haemodynamic (impaired auto regulation and hyperperfusion) and through VEGF (vascular endothelial growth factor). This hypothesis has been supported by observations from clinical studies which showed an association between hypertension and the presence and severity of retinopathy in people with diabetes[38,40].

The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure[41], while in the WESDR, diastolic blood pressure was a significant predictor of progression of diabetic retinopathy to PDR over 14 yr of follow up in patients type 1 diabetes[35]. In the Indian context, hypertension was not a significant confounding factor in the CURES Eye study, however uncontrolled hypertension did influence the progression of DR[10].

Renal disease: A link between renal and retinal angiopathy in diabetes has been long recognized, an effect that may be mediated through an increase in blood pressure, fibrinogen levels and lipoproteins[42]. Cross-sectional[43] and longitudinal studies[44,45] report a relationship between microalbuminuria, proteinuria and retinopathy. Proteinuria was present in 29.2 per cent of the subjects with DR in the CURES Eye study[10], while studies from north India[46,47] have

Table II. Risk factors associated with the development of diabetic retinopathy

Systemic factors	Ocular factors
Gender	Posterior vitreous detachment
Duration of diabetes	
Glycaemic control	Old chorioretinopathy
Hypertension	Cataract surgery
Renal disease	
Elevated serum lipids	
Pregnancy	
Alcohol	
Anaemia	
Obesity	

Table III. Potential molecules for the management of diabetic retinopathy

Agent	Molecules tried
Anti-platelet or anticoagulant agents	Aspirin[88]
Anti-platelet agents	Ticlopidine[89]
Aldose reductase inhibitors	Ponalrestat[90]
	Tolrestat[91]
Growth hormone suppressors	Octreotide[92]
Anti angiogenic agent	Curcumin[87]
Angiotension-converting	Candesartan cilexetil[93]
enzyme inhibitors	Perinodopril[94]
PKCβ inhibitors	Ruboxistaurin (LY333531)[95]
	PKC412 [96]

PKC, protein kinase C

suggested a correlation between DR and microalbuminuria. Mohan *et al*[48] reported that the prevalence of proliferative retinopathy was significantly higher in type 2 south Indian diabetic patients with macroproteinuria (35%) compared with those with microproteinuria (4%). A recent study done by Klein *et al*[49] demonstrated a significant association between DR and preclinical morphologic changes of diabetic nephropathy in type 1 diabetic patients.

Elevated serum lipids: Individuals with elevated total serum cholesterol, low-density lipoprotein (LDL) cholesterol or triglyceride levels are more likely to have or develop retinal hard exudates, which can be associated with risk of vision loss, independent of the extent of macular oedema[50]. Several investigators have reported on the association of lipids with DR, but the results have not been consistent. The ETDRS[51] and the WESDR group[52] found a statistically significant association between elevated serum total cholesterol and LDL cholesterol and the severity of retinal hard exudation in patients with DR.

Rema *et al*[53] in an earlier study showed an association of DME in type 2 diabetic subjects with increased LDL levels. Other studies have demonstrated that decreasing dietary polyunsaturated fats may have an association with shrinkage of exudates and a treatment apt to lower plasma lipid levels reduced the risk size of perimacular hard exudates. It has also been shown that in type 2 diabetic subjects there was an increase in the lipid peroxidation in plasma and this is accentuated in patients with diabetic complications[54]. A recent paper from the CURES eye study[55] showed an association of DR with total cholesterol and serum triglycerides. This association was maintained even after adjusting for age, as age by itself is a significant risk factor for hyperlipidaemia. The other significant finding in type 2 diabetes was that DME also showed a strong correlation with high LDL levels in the study.

Pregnancy: It is recognized that DR can progress rapidly during pregnancy due to hormonal changes. The progression is usually transient and the long term risk of progression of DR does not appear to be increased by pregnancy[56]. The factors associated with progression of DR include the pregnant state itself, duration of diabetes, amount of retinopathy at conception, blood glucose control, and the presence of coexisting vascular disease[57]. There is a paucity of published data on the role of pregnancy as a risk factor for DR in Indians. Studies conducted in western population report that progression of all stages of DR can occur in pregnant women with uncontrolled diabetes mellitus. Both the DCCT[56] and the Diabetes in Early Pregnancy Study[58] reported that women with the poorest glycaemic control at baseline in the 1st trimester were at increased risk of DR progression.

Alcohol: A few studies have examined the effect of alcohol consumption on DR. Young *et al*[59] reported heavy alcohol consumption to be a risk factor for development of DR in patients without retinopathy at baseline. The Casteldaccia Eye Study[60] demonstrated that duration of alcohol intake was associated with DR. In contrast, WESDR showed no significant association with incidence or progression of retinopathy[61].

Anaemia: Anaemia is considered another risk factor, perhaps because of smaller amounts of oxygen for the retinal tissue[62]. Singh *et al*[63] reported spontaneous closure of the microaneurysms on correction of anaemia and metabolic control in type 1 diabetic patient with coexisting nutritional anaemia. In the ETDRS, low haematocrit was an independent risk factor for development of high risk PDR and visual impairment[64]. A Finnish study[65] showed that the odds ratio of having any retinopathy was two-fold among subjects with a haemoglobin level of less than 12 g/dl, as compared with those having a higher haemoglobin level, even after controlling for serum creatinine levels, proteinuria, and other prognostic factors associated with diabetes. In addition, DR patients with low haemoglobin levels, had over five-fold increased risk of severe retinopathy compared to those with higher haemoglobin levels.

Obesity: Recent studies have shown that DR may not only be associated with glycaemic control and blood pressure, but also to body mass index (BMI) in patients with type 2 diabetes[66,67]. Perhaps variation in ethinicity may explain the fact that BMI did not manifest as a risk factor for DR in the CURES Eye study. On the contrary subjects with type 2 diabetes and PDR had a lower BMI[10]. Zhang *et al*[68] in the diabetes control and complications trial (DCCT) observed that besides diabetes duration and metabolic control, BMI had a significant predictive value in developing retinopathy.

Ocular factors

Posterior vitreous detachment (PVD) is a phenomenon, which occurs due to degenerative changes in the vitreous and significantly more common in diabetic subjects. It has been shown that a complete PVD may prevent the development of PDR because the hyaloid is needed as a scaffold for retinal neovascularization[69]. An attached posterior hyaloid has also been associated with an increased risk for DME[70].

High myopia with choroidal degeneration and extensive old chorioretinopathy protect against DR and are believed to act in the same manner as pan retinal photocoagulation by reducing the metabolic needs of the retina[71].

Removal of a cataract may aggravate both existing DME and NPDR and may hasten the onset of rubeosis[72]. In the Palakkad Eye Disease Survey, which looked at visual impairment and blindness in the population reported that cataract (27.8%) was one of the major causes for visual disability among subjects with diabetes[13]. In a retrospective analysis done in 223 eyes of 184 type 2 diabetic subjects who underwent cataract surgery, it has been reported that 44 per cent had progression of DR after cataract surgery and 8.0 per cent developed DR for the first time, this was mainly in patients who underwent extra capsular cataract extraction with intra ocular lens (IOL) implantation[73] [Presented at the Vitreo-Retinal Society of India. Annual Conference, Goa, 2002]. This emphasizes the need of routine retinal documentation and detecting DR before cataract extraction.

Other factors

In addition to systemic and ocular factors, recent studies in western population have shown that DR is associated with atherosclerotic end points[73,74]. The CURES study, which assessed the association of intima-media thickness (IMT) and arterial stiffness (AI) with diabetic retinopathy in 590 south Indian population demonstrated that IMT and AI showed a significant association with diabetic retinopathy, even after adjusting for age, duration of diabetes, HbA_{1c}, serum cholesterol, serum triglycerides, and microalbuminuria[75]. This association suggests that common pathogenic mechanisms might predispose to diabetic micro- and macroangiopathy.

The role of oxidant stress in the causation of DR is increasingly being recognized[76,77]. Very recently it has also been shown that hypoglutathionaemia and increased oxidative stress appear to be early biochemical aberrations in diabetes, and through protein alterations, oxidative stress and redox modifications may contribute to pathogenesis of diabetic microangiopathy[78]. Increased erythrocyte glutathionylated Hb (HbSSG) levels with decreased glutathione (GSH) was shown to be associated with DR indicating that the increased oxidative stress may be one of the implicating factors in the pathogenesis of DR[79].

The role of genetic factors in susceptibility to retinopathy has been studied recently as some patients develop DR despite good control and others escape retinopathy despite poor control[80,81]. In a study conducted in 322 type 2 diabetic families, Rema *et al*[80] 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.

It has also been demonstrated that in Mexican-American type 2 diabetic siblings of probands with DR, severity of DR aggregates in families rather than the presence of DR itself[81].

Screening and management

As individuals with sight-threatening retinopathy (PDR and DME) may not have symptoms, life-long evaluation for retinopathy by retinal screening of diabetic individuals is a valuable and necessary strategy. Screening strategies depend on the rate of appearance and progression of diabetic retinopathy and on the risk factors that alter these rates. The retina may be examined by ophthalmoscopy and slit lamp biomicroscopy using 78 D lens, or by using retinal photography[82]. It has been shown that seven-standard field stereoscopic 30° fundus photography is the gold standard for assessing DR, however digital colour photography have now replaced this cumbersome mode of screening. Recently several new, noninvasive techniques promise to improve diagnostic sensitivity, one such technique is the optical coherence tomography (OCT). This method co-relates well with fundus fluorescein angiography (FFA)[83].

Laser photocoagulation and vitrectomy have improved the quality of life for patients with DR and prevented debilitating visual loss[84,85]. In a study conducted in 261 eyes of 160 type 2 diabetic subjects with PDR who underwent pan retinal photocoagulation (PRP), 73 per cent eyes maintained >6/9 at 1 yr follow up[38]. However, laser photocoagulation and vitrectomy are indicated only when DR has progressed to a measurably advanced stage in which some visual loss has already occurred. Because of these limitations of current management strategies, new pharmacological therapies are being developed; targeting the fundamental pathogenic mechanisms that initiate or sustain the progression of DR. Currently recalcitrant DME has been treated with moderate success by intra-vitreal injections of steroids[86].

Various antiproliferative agents which have been tried in anti-cancer therapy, are being tried in PDR. Curcumin (diferuloylmethane) an active ingredient of turmeric, has been tried successfully as an antiproliferative agent. The effect of curcumin on human retinal endothelial cells (HERCs) exposed to high glucose has been published recently[87]. It was demonstrated that curcumin inhibited the proliferation of HERCs, in a dose-dependent manner by inducing cell death in HRECs cultured with high glucose conditions. The authors also suggest that curcumin reduces proliferation of HRECs by decreasing VEGF expression/release and VEGF mediated PKC βII translocation. Table III summarizes various molecules tried in DR management[87-96].

Conclusions

As new therapies for DR and its associated complications emerge, the need to collect and monitor new epidemiological data becomes increasingly important to be able to evaluate the impact and effectiveness of these therapies. Although urban Indian population based studies suggest that the prevalence of DR is lower compared to other ethnic groups, given the large number of diabetic subjects in India (31.7 million), even with the lower prevalence rates (17.6%), this would translate to over 5.6 million subjects with DR. This underscores the need for routine retinal screening of diabetic individuals annually to detect DR and prevent visual impairment. In addition, optimized control of systemic considerations, which affect onset and/or progression of DR, through an intensive, multi-disciplinary, healthcare team-based approach, can markedly reduce impairment of vision due to DR.

References

1. Aiello LP, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, *et al*. Diabetic retinopathy. *Diabetes Care* 1998; *21* : 143-56.

2. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1984; *102* : 520-6.

3. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984; *102* : 527-32.

4. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. *Ophthalmology* 1984; *91* : 1-9.

5. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; *27* : 1047-53.

6. Abrahamian H, Hornlein B, Gurdet C, Willinger C, Zaruba E, Irsigler K.Insulin-dependent diabetes mellitus:"EURODIAB IDDM Complications Study"-results from the Vienna center. *Wien Klin Wochenschr* 1994; *106* : 136-40.

7. Mohan R, Mohan V, Ramachandran A, Viswanathan M. Retinopathy in insulin dependent diabetes mellitus (IDDM) in south India. *J Assoc Physicians India* 1989; *37* : 370-3.

8. Rema M, Mohan V. Retinopathy at diagnosis among young Asian diabetic patients- ASDIAB Study Group. *Diabetes* 2002; *51* (Suppl 2) : A206-7.

9. Rema M, Ponnaiya M, Mohan V. Prevalence of retinopathy in non insulin dependent diabetes mellitus at a diabetes centre in southern India. *Diabetes Res Clin Pract* 1996; *34* : 29-36.

10. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: The Chennai Urban Rural Epidemiology Study (CURES) Eye Study, I. *Invest Ophthalmol Vis Sci* 2005; *46* : 2328-33.

11. Deepa M, Pradeepa R, Rema M, Mohan A, Deepa R, Shanthirani S, *et al*. The Chennai Urban Rural Epidemiology Study (CURES) - study design and Methodology (Urban component) (CURES - 1). *J Assoc Physicians India* 2003; *51* : 863-70.

12. Dandona L, Dandona R, Naduvilath TJ, McCarty CA, Rao GN. Population based assessment of diabetic retinopathy in an urban population in southern India. *Br J Ophthal* 1999; *83* : 937-40.

13. Narendran V, John RK, Raghuram A, Ravindran RD, Nirmalan PK, Thulasiraj RD. Diabetic retinopathy among self reported diabetics in southern India: a population based assessment. *Br J Ophthalmol* 2002; *86* : 1014-8.

14. Rema M, Shanthirani CS, Deepa R, Mohan V. Prevalence of diabetic retinopathy in a selected South Indian Population - The Chennai Urban Population Study (CUPS). *Diabetes Res Clin Pract* 2000; *50* : S252.

15. Connolly V, Unwin N, Sherriff P, Bilous R, Kelly W. Diabetes, prevalence and socioeconomic status: a population based study showing increased prevalence of Type 2 diabetes in the deprived areas. *J Epidemiol Commun Health* 2000; *54* : 173-7.

16. Harris MI. Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 1993; *16* : 642-52.

17. Rema M, Deepa R, Mohan V. Prevalence of retinopathy at diagnosis among Type 2 diabetic patients attending a diabetic centre in South India. *Br J Ophthalmol* 2000; *84* : 1058-60.

18. Ramachandran A, Snehalatha C, Vijay V, Viswanathan M. Diabetic retinopathy at the time of diagnosis of NIDDM in south Indian subjects. *Diabetes Res Clin Pract* 1996; *32* : 111-4.

19. Kohner EM, Aldington SJ, Stratton IM, Manley SE, Holman RR, Matthews DR, *et al*. Diabetic retinopathy at diagnosis of non insulin dependent diabetes mellitus and associated risk factors. United Kingdom Prospective Diabetes Study, 30. *Arch Ophthalmol* 1998: *116* : 297-303.

20. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. *Diabetes Care* 1992; *15* : 815-9.

21. Owens DR, Volund E, Jones D, Shannon AG, Jones IR, Birtwell AJ, *et al*. Retinopathy in newly presenting non insulin dependent (type 2) diabetic patients. *Diabetes Res Clin Pract* 1988; *9* : 59-65.

22. Klein R, Klein BEK, Moss SE, Linton KL. The Beaver Dam study: retinopathy in adults with newly discovered and previously diagnosed diabetes mellitus. *Ophthalmology* 1992; *99* : 58-62.

23. Varma R, Torres M, Pena F, Klein R, Azen SP, Los Angeles Latino Eye Study Group Prevalence of diabetic retinopathy in adult Latinos: the Los Angeles Latino eye study. *Ophthalmology* 2004; *111* : 1298-306.

24. Broadbent DM, Scott JA, Vora JP, Harding SP. Prevalence of diabetic eye disease in an inner city population: the Liverpool Diabetic Eye Study. *Eye* 1999; *13* : 160-5.

25. Leske MC, Wu SY, Hyman L, Li X, Hennis A, Connell AM, *et al*. Diabetic retinopathy in a black population: the Barbados Eye Study. *Ophthalmology* 1999; *106* : 1893-9.

26. Mitchell P, Smith W, Wang JJ, Attebo K. Prevalence of diabetic retinopathy in an older community: the Blue Mountains Eye Study. *Ophthalmology* 1998; *105* : 406-11.

27. Chen MS, Kao CS, Chang CJ, Wu TJ, Fu CC, Chen CJ, *et al*. Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects. *Am J Ophthalmol* 1992; *114* : 723-30.

28. Klein R, Klein BE, Moss SE, Linton KL. The Beaver Dam Eye Study. Retinopathy in adults with newly discovered and previously diagnosed diabetes mellitus. *Ophthalmology* 1992; *99* : 58-62.

29. The Eye Diseases Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol* 2004; *122* : 552-63.

30. Agardh E, Agardh CD. Diabetic retinopathy. In: Defronzo RA, Ferrannini E, Keen H, Zimmet P, editors. *International textbook of diabetes mellitus*. 3rd ed. Vol. 2. Chichester, England: John Wiley; 2004 p. 1187-206.

31. Balasubramanyam M, Rema M, Premanand C. Biochemical and molecular mechanisms of diabetic retinopathy. *Curr Sci* 2002; *83* : 1506-14.

32. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; *414* : 813-20.

33. Aiello LM, Rand LI, Briones JC, Wafai MZ, Sebestyen JG. Diabetic retinopathy in Joslin Clinic patients with adult-onset diabetes. *Ophthalmology* 1981; *88* : 619-23.

34. Klein R, Davis MD, Moss SE, Klein BE, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. A comparison of retinopathy in younger and older onset diabetic persons. *Adv Exp Med Biol* 1985; *189* : 321-35.

35. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in Type 1 diabetes. *Ophthalmology* 1998; *105* : 1801-15.

36. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; *329* : 977-86.

37. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; *352* : 837-53.

38. Rema M, Sujatha P, Pradeepa R. Visual outcomes of pan-retinal photocoagulation in diabetic retinopathy at one-year follow-up and associated risk factors. *Indian J Ophthalmol* 2005; *53* : 93-9.

39. Kohner EM. Diabetic retinopathy. *Br Med Bull* 1989; *45* : 148-73.

40. Fujisawa T, Ikegami H, Yamato E, Kawaguhi Y, Ueda H, Shintani M, *et al*. Association of plasma fibrinogen level and blood pressure with diabetic retinopathy and renal complications associated with proliferative diabetic retinopathy in type II diabetes mellitus. *Diabet Med* 1999; *16* : 522-6.

41. Kostraba JN, Klein R, Dorman JS, Becker DJ, Drash AL, Maser RE, *et al*. The Epidemiology of Diabetes Complications Study. IV. Correlates of diabetic background and proliferative retinopathy. *Am J Epidemiol* 1991; *133* : 381-91.

42. Root HF, Pote WH Jr, Frehner H. Triopathy of diabetes; sequence of neuropathy, retinopathy, and nephropathy in one hundred fifty-five patients. *AMA Arch Intern Med* 1954; *94* : 931-41.

43. Cruickshanks KJ, Ritter LL, Klein R, Moss SE. The association of microalbuminuria with diabetic retinopathy. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Ophthalmology* 1993; *100* : 862-7.

44. Klein R, Moss SE, Klein BE. Is gross proteinuria a risk factor for the incidence of proliferative diabetic retinopathy? *Ophthalmology* 1993; *100* : 1140-6.

45. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T. The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. *Diabet Med* 1995; *12* : 482-7.

46. Gupta DK, Verma LK, Khosla PK, Dash SC. The prevalence of microalbuminuria in diabetes: a study from north India. *Diabetes Res Clin Pract* 1991; *12* : 125-8.

47. Singh SK, Behre A, Singh MK. Diabetic retinopathy and microalbuminuria in lean type 2 diabetes mellitus. *J Assoc Physicians India* 2001; *49* : 439-41.

48. Mohan V, Meera R, Premalatha G, Deepa R, Miranda P, Reema M. Frequency of proteinuria in type 2 diabetes mellitus seen at a diabetes centre in southern India. *Postgrad Med J* 2000; *76* : 569-73.

49. Klein R, Zinman B, Gardiner R, Suissa S, Donnelly SM, Sinaiko AR, *et al*. The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: the Renin-Angiotensin System Study. *Diabetes* 2005; *54* : 527-33.

50. Chew EY, Klein ML, Ferris FL III, Remaley NA, Murphy RF, Chantry K, *et al*. Association of elevated serum lipid levels with retinal hard exudates in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) report 22. *Arch Ophthalmol* 1996; *114* : 1079-84.

51. Ferris FL 3rd, Chew KY, Hoogwerf BJ. Serum lipids and diabetic retinopathy. Early Treatment Diabetic Retinopathy Study Research Group. *Diabetes Care* 1996; *19* : 1291-3.

52. Klein BEK, Moss SE, Klein R, Surawicz TS. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XIII: relationship between serum cholesterol to retinopathy and hard exudate. *Ophthalmology* 1991; *98* : 1261-5.

53. Mohan R, Mohan V, Susheela L, Ramachandran A, Viswanathan M, *et al*. Increased LDL cholesterol in non-insulin dependent diabetes with maculopathy. *Acta Diabetol Lat* 1984; *21* : 85-9.

54. Sundaram RK, Bhaskar A, Vijayalingam S, Viswanathan M, Rema M, Shanmugasundram KR. Antioxidant status and lipid peroxidation in type II diabetes mellitus with and without complications. *Clin Sci* 1996; *90* : 255-60.

55. Rema M, Srivastava BK, Anitha B, Deepa R, Mohan V. Association of serum lipids with diabetic retinopathy in urban south Indians - The Chennai Urban Rural Epidemiology Study (CURES) Eye Study-2. *Diab Med* 2005; *23* : 1029-36.

56. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes Care* 2000; *23* : 1084-91.

57. Sheth BP. Does pregnancy accelerate the rate of progression of diabetic retinopathy? *Curr Diab Rep* 2002; *2* : 327-30.

58. Chew EY, Mills JL, Metzger BE, Remaley NA, Jovanovic-Peterson L, Knopp RH, *et al*. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. *Diabetes Care* 1995; *18* : 631-7.

59. Young RJ, McCulloch DK, Prescott RJ, Clarke BF. Alcohol: another risk factor for diabetic retinopathy? *Br Med J (Clin Res Ed)* 1984; *288* : 1035-7.

60. Giuffre G, Lodato G, Dardanoni G. Prevalence and risk factors of diabetic retinopathy in adult and elderly subjects: The Casteldaccia Eye Study. *Graefes Arch Clin Exp Ophthalmol* 2004; *242* : 535-40.

61. Moss SE, Klein R, Klein BE. The association of alcohol consumption with the incidence and progression of diabetic retinopathy. *Ophthalmology* 1994; *101* : 1962-8.

62. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA* 1988; *260* : 2864-71.

63. Singh R, Gupta V, Gupta A, Bhansali A. Spontaneous closure of microaneurysms in diabetic retinopathy with treatment of co-existing anaemia. *Br J Ophthalmol* 2005; *89* : 248-9.

64. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, *et al*. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. *Invest Ophthalmol Vis Sci* 1998; *39* : 233-52.

65. Qiao Q, Keinanen-Kiukaanniemi S, Laara E. The relationship between hemoglobin levels and diabetic retinopathy. *J Clin Epidemiol* 1997; *50* : 153-8.

66. Katusic D, Tomic M, Jukic T, Kordic R, Sikic J, Vukojevic N, *et al*. Obesity - a risk factor for diabetic retinopathy in type 2 diabetes? *Coll Antropol* 2005; *29* (Suppl 1) : 47-50.

67. van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, *et al*. Blood pressure, lipids, and obesity are associated with retinopathy: the Hoorn study. *Diabetes Care* 2002; *25* : 1320-5.

68. Zhang L, Krentowski G, Albert A, Lefebvre PJ. Risk of developing retinopathy in Diabetes Control and Complications Trial type 1 diabetic patients with good or poor metabolic control. *Diabetes Care* 2001; *24* : 1275-9.

69. Akiba J, Arzabe CW, Trempe CL. Posterior vitreous detachment and neovascularization in diabetic retinopathy. *Ophthalmology* 1990; *97* : 889-91.

70. Lewis H, Abrams GW, Blumenkranz MS, Campo RV. Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction. *Ophthalmology* 1992; *99* : 753-9.

71. Moss SE, Klein R, Klein BE. Ocular factors in the incidence and progression of diabetic retinopathy. *Ophthalmology* 1994; *101* : 77-83.

72. Schatz H, Atienza D, McDonald HR, Johnson RN. Severe diabetic retinopathy after cataract surgery. *Am J Ophthalmol* 1994; *117* : 314-21.

73. Kim YH, Hong MK, Song JM, Han KH, Kang DH, Song JK, *et al*. Diabetic retinopathy as a predictor of late clinical events following percutaneous coronary intervention. *J Invasive Cardiol* 2002; *14* : 599-602.

74. Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, *et al*. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Arch Intern Med* 2004; *164* : 1917-24.

75. Rema M, Mohan V, Deepa R, Ravikumar R. Association of carotid intima-media thickness and arterial stiffness with diabetic retinopathy. The Chennai Urban Rural Epidemiology Study (CURES-2). *Diabetes Care* 2004; *27* : 1962-7.

76. Anusha P, Vijayalingam S, Shanmugasundaram R, Rema M. Oxidative stress and the development of diabetic complications - Antioxidants and lipid peroxidation in erythrocytes and cell membrane. *Cell Biol Int* 1995; *19* : 987-93.

77. Rema M, Mohan V, Anusha B, Shanmugasundaram R. Does oxidant stress play a role in diabetic retinopathy. *Indian J Ophthalmol* 1995; *43* : 17-21.

78. Sampathkumar R, Balasubramanyam M, Tara C, Rema M, Mohan V. Association of hypoglutathionemia with reduced Na(+)/K(+) ATPase activity in type 2 diabetes and microangiopathy. *Mol Cell Biochem* 2006; *282* : 169-76.

79. Sampathkumar R, Balasubramanyam M, Sudarslal S, Rema M, Mohan V, Balaram R. Increased glutathionylated hemoglobin (HbSSG) in type 2 diabetes subjects with microangiopathy. *Clin Biochem* 2005; *38* : 892-9.

80. Rema M, Saravanan G, Deepa R. Familial clustering of diabetic retinopathy in South Indian Type 2 diabetic patients. *Diabet Med* 2002; *19* : 910-6.

81. Hallman DM, Huber JC Jr, Gonzalez VH, Klein BE, Klein R, Hanis CL. Familial aggregation of severity of diabetic retinopathy in Mexican Americans from Starr County Texas. *Diabetes Care* 2005; *28* : 1163-8.

82. Viswanath K. Diabetic retinopathy: Clinical findings and management. *Commun Eye Health J* 2003; *16* : 21-4.

83. Bijlsma WR, Stilma JS. Optical coherence tomography, an important new tool in the investigation of the retina. *Ned Tijdschr Geneeskd* 2005; *149* : 1884-91.

84. Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis. *Curr Opin Ophthalmol* 2000; *11* : 175-9.

85. Sharma S, Hollands H, Brown GC, Brown MM, Shah GK, Sharma SM, *et al*. The cost-effectiveness of early vitrectomy for the treatment of vitreous hemorrhage in diabetic retinopathy. *Curr Opin Ophthalmol* 2001; *12* : 230-4.

86. Massin P, Audren F, Haouchine B, *et al*. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema. *Ophthalmology* 2004; *11* : 218-25.

87. Premanand C, Rema M, Sameer Mahmood Z, Sujatha M, Balasubramanyam M. Effect of curcumin on proliferation of human retinal endothelial cells under *in vitro* conditions. *Invest Ophthalmol Vis Sci* 2006; *47* : 2179-84.

88. The Early Treatment Diabetic Retinopathy Study Research Group: Effects of aspirin treatment on diabetic retinopathy. ETDRS report number 8. *Ophthalmology* 1991; *98* (5 Suppl) : 757-65.

89. The TIMAD Study Group: Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy. *Arch Ophthalmol* 1990; *108* : 1577-83.

90. Arauz-Pacheco C, Ramirez LC, Pruneda L, Sanborn GE, Rosenstock J, Raskin P, *et al*. The effect of the aldose reductase inhibitor, ponalrestat, on the progression of diabetic retinopathy. *J Diabetes Complications* 1992; *6* : 131-7.

91. Van Gerven JM, Boot JP, Lemkes HH. Effects of aldose reductase inhibition with tolrestat on diabetic retinopathy in a six months double blind trial. *Doc Ophthalmol* 1994; *87* : 355-65.

92. Grant MB, Mames RN, Fitzgerald C, Hazariwala KM, Cooper-Dettoff R, Caballero S, *et al*. The efficacy of octreotide in the therapy of severe nonproliferative and early proliferative diabetic retinopathy: a randomized controlled study. *Diabetes Care* 2000; *23* : 504-9.

93. Chaturvedi N, Sjoelie AK, Svensson A. DIRECT Programme Study Group. The Diabetic Retinopathy Candesartan Trials (DIRECT) Programme, rationale and study design. *J Renin Angiotensin Aldosterone Syst* 2002; *3* : 255-61.

94. ADVANCE Collaborative Group. ADVANCE - Action in diabetes and vascular disease: patient recruitment and characteristics of the study population at baseline. *Diabet Med* 2005; *22* : 882-8.

95. The PKC-DRS Study Group:The effect of Ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy: Initial results of the protein kinase C {beta} inhibitor diabetic retinopathy study (PKC-DRS) Multicenter Randomized Clinical Trial. *Diabetes* 2005; *54* : 2188-97.

96. Campochiaro PA. C99-PKC412-003 Study Group. Reduction of diabetic macular edema by oral administration of the kinase inhibitor PKC412. *Invest Ophthalmol Vis Sci* 2004; *45* : 922-31.

Reprint requests: Dr M. Rema, Consultant Ophthalmologist & Director, Madras Diabetes Research Foundation
4, Conran Smith Road, Gopalapuram, Chennai 600086, India
e-mail: drrema@vsnl.com