Review Article

Diabetic retinopathy: An update

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Diabetes mellitus is a major cause of avoidable blindness in both the developing and the developed countries. Significant technological advances have taken place to improve the diagnostic accuracy of diabetic retinopathy. In the last three decades, the treatment strategies have been revised to include, besides laser photocoagulation, early surgical interventions and pharmacotherapies.

Key words: Diabetic macular edema, diabetic retinopathy, laser photocoagulation, pars plana vitreous surgery

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Diabetes mellitus (DM) is a major cause of avoidable blindness in both the developing and the developed countries. Patients with diabetic retinopathy (DR) are 25 times more likely to become blind than non-diabetics.[1] Good glycemic control arrests the development and progression of DR and decreases the visual loss. Technological advances have improved the diagnostic accuracy of screening methods and access of the diabetic patients to the specialist care. In the last three decades, the treatment strategies have been revised to include, besides laser photocoagulation, early surgical interventions and pharmacotherapies. The aim of this review was to outline the magnitude of problem of DR in India with the current strategies to manage it.

Epidemiology

Majority of the patients have non-insulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes. The prevalence of insulin-dependent diabetes mellitus (IDDM) or type 1 diabetes is 10-15% of the diabetic population. Prevalence of DR in Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) was 50.1%[2] and 54.2% in the diabetes control and complications trial (DCCT) in IDDM[3] and 35-39% in United Kingdom Prospective Diabetes Study (UKPDS)[4] in NIDDM. In two studies from South India, the prevalence rates of DR in NIDDM patients were 34.1% and 37%.[5,6] India has 31.7 million diabetic subjects at present as per the World Health Organization (WHO) estimates.[7] In the Andhra Pradesh Eye Disease Study (APEDS) of self-reported diabetics, the prevalence of DR was 22.4%.[8] In the Chennai Urban Rural Epidemiology Study (CURES), we evaluated urban sample of diabetic patients and estimated the overall prevalence of DR as 17.6%.[9]

Prevalence of Visual Impairment Related to Diabetic Retinopathy

In WESDR, 1.4% of IDDM patients had best-corrected visual acuity of 20/80 to 20/160; and 3.6% had acuity 20/200 or worse in the better eye.[10] In the older-onset group, 3% had vision in the range 20/80 to 20/160; and 1.6% were 20/200 or worse in the better eye.[10]

Incidence

After 10 years of onset of DM, blindness (visual acuity of 20/200 or less in the better eye) was 1.8, 4.0 and 4.8% in type 1, insulin-treated type 2 and non-insulin-treated type 2 patients, respectively.[11] In these three groups of patients, the 10-year incidence visual impairment (loss of 15 letters on a scale of 0-70 letters) was 9.4, 37.2 and 23.9%, respectively.[11]

Pathophysiology

The final metabolic pathway causing DR is unknown. There are several theories. Electrolytic imbalance caused by the high aldose reductase levels leads to cell death, especially retinal pericytes, which cause microaneurysm formation.[12] Apart from this, thickening of the capillary basement membrane and increased deposition of extracellular matrix components contribute to the development of abnormal retinal hemodynamics.[13] In diffuse type of diabetic macular edema (DME), breakdown of the inner blood-retinal barrier results in accumulation of extracellular fluid.[14]

Increased retinal leukostasis has been reported and it causes capillary occlusions and dropout, non-perfusion, endothelial cell damage and vascular leakage due to its less deformable nature.[15]

Currently, there has been a great interest in vasoproliferative factors, which induce neovascularization. It has been shown that retinal ischemia stimulates a pathologic neovascularization mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), which results in proliferative diabetic retinopathy (PDR).[16] VEGFs are released by retinal pigment epithelium, pericytes and endothelial cells of the retina.

Risk Factors

Duration of diabetes

There is a direct correlation between the frequency and severity of DR and the duration of DM.[17]

Glycemic control

There is an indirect relationship between the glycemic control

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and the development and progression of DR. DCCT and Early Treatment of Diabetic Retinopathy Study (ETDRS) have convincingly shown the reduction in risk of progression of DR with intensive treatment. Decrease in glycosylated hemoglobin levels was associated with a significant decrease in the progression of DR as well as the incidence of PDR.[18] Intensive diabetic control leads to reduction in the development and progression of all diabetic complications.[19]

Age and sex

The prevalence and severity of DR increases with increasing age in type 1 DM but not in type 2 DM.[17]

Hypertension

Studies, such as WESDR and UKPDS, suggest that hypertension increases the risk and progression of DR and DME. In UKPDS, tight control of blood pressure resulted in 34% reduction in progression of retinopathy with 47% reduced risk of deterioration in visual acuity of three lines.

Nephropathy

The presence of gross proteinuria at baseline has been reported to be associated with 95% increased risk of developing DME among type I patients in the WESDR. The prevalence of PDR was much higher in patients with persistent microalbuminuria.[20]

Genetics

In WESDR, patients with HLA DR4 and absent HLA DR3 were found to be at a greater risk of having PDR. Data from the DCCT also suggested genetic predisposition to diabetes. However, it is probable that both genetic and environmental factors play a role in the expression of DR.[21]

Serum lipid

In WESDR, higher total serum cholesterol was associated with increased risk of having retinal hard exudates. ETDRS has reported a positive correlation between serum lipids and risk of retinal hard exudates in type 2 DM. Recently, Gupta *et al.* have reported reduction in edema, severity of hard exudates and subfoveal lipid migration in patients with type 2 diabetes and dyslipidaemia, using a lipid-lowering drug, atorvastatin, as an adjunct to macular photocoagulation.[22]

Anemia

In ETDRS, low hematocrit levels at baseline were identified as independent risk factor for the development of high-risk PDR and severe visual loss. It showed an increased risk of retinopathy in patients with the hemoglobin level of less than 12 g/dl.[23] Anemia-induced retinal hypoxia is speculated as cause of development of microaneurysms and other retinopathy changes.[24]

Puberty

In WESDR, younger onset subjects who were post-menarchal stood a 3.2 times greater risk of developing DR as compared to pre-menarchal subjects.[25] Those who were older than 13 years at the time of diagnosis were more likely to have retinopathy than those who were younger. The exact mechanism by which puberty might exert its effect on the development of early retinopathy is not yet understood, but a possible role of hormonal factors is suspected.

Socioeconomic status

Although educational attainment was inversely associated with retinopathy in women in the WESDR, socioeconomic status was not associated with increased risk of worsening of retinopathy. Once the level of glycemia is accounted for, social factors have little or no influence on this complication of diabetes.[26]

Pregnancy

Pregnant women with type 1 diabetes have twice the risk of developing PDR than non-pregnant women. Ideally, young mothers should be examined for retinopathy before the onset of pregnancy.[27] The cause of acceleration of DR may be a simple reflection of long duration of diabetes[28,29] or there may be factors, both metabolic and hormonal, that contribute to the overall deterioration of DR in the pregnant patient.

Clinical Features of Diabetic Retinopathy

Non-proliferative and proliferative diabetic retinopathy

Non-proliferative diabetic retinopathy (NPDR) is characterized by the presence of: (i) microaneurysms, which are the first clinically detectable lesions of DR located in the inner nuclear layer of the retina, (ii) dot and blot hemorrhages, which are located in the middle retinal layers, (iii) hard exudates, which are located between the inner plexiform and inner nuclear layer of the retina, (iv) vascular changes such as beading, looping and sausage like segmentation of the veins, (v) cotton wool spots, also called soft exudates or nerve fiber infarcts, result from capillary occlusion of the retinal nerve fiber layer, (vi) intraretinal microvascular abnormalities (IRMA), which are dilated capillaries that seem to function as collateral channels, frequently seen adjacent to the areas of capillary closure, (vii) retinal edema characterized by accumulation of fluid between the outer plexiform layer and inner nuclear layer, which may later involve the entire layers of the retina.

In the natural course, approximately 50% of patients with very severe NPDR progress to PDR within 1 year.[30] PDR is characterized by the presence of neovascularization. New vessels may proliferate on the optic nerve head (new vessels at disc - NVD) and along the course of the major vascular arcades (new vessels elsewhere - NVE). The new vessels mostly grow along the posterior hyaloid and sudden vitreous contraction may result in rupture of these fragile vessels. When the vitreous detachment occurs, the new vessels are pulled anteriorly along with the underlying retina, resulting in tractional retinal detachment. On the other hand, vitreous might detach completely without any pull on the retina and new vessels regress, thus resulting in the development of an end-stage disease.

ETDRS[31] has classified NPDR into mild, moderate, severe and very severe and PDR into early PDR and high-risk PDR. This is as follows:

A. Mild NPDR: Presence of at least one microaneurysm, definition not met for B, C, D, E, or F.
B. Moderate NPDR: Hemorrhages and/or microaneurysms more than standard photo 2A, presence of soft exudates, venous beading, IRMA definitely present, definition not met for C, D, E, or F.
C. Severe NPDR: Hemorrhages and/or microaneurysms more than standard photo 2A in all four quadrants, or venous beading in two or more quadrants, or IRMA > standard photo 8A in at least one quadrant, definition not met for

D, E, or F.

D. Very severe NPDR: Any two or more of the changes seen in severe NPDR, definition not met for E, or F.
E. Early PDR: Presence of new vessels, definition not met for F.
F. High-risk PDR: Includes any of the following characteristics - neovascularization of disc (NVD) > 1/3rd to 1/4th disc diameter, NVD < 1/3rd to 1/4th disc diameter with vitreous/pre-retinal hemorrhage, NVE with vitreous/pre-retinal hemorrhage. High-risk characteristics (HRC) were defined by DRS, as the patient, if not treated urgently, is at a high risk of severe visual loss.

International Clinical Diabetic Retinopathy Disease Severity scale[32] has developed an easily understandable scale to classify NPDR. This scale is based on findings observed upon dilated ophthalmoscopy, which includes no apparent retinopathy - no abnormalities, mild NPDR - microaneurysms only, moderate NPDR - more than just microaneurysms but less than severe NPDR and severe NPDR includes any of the following such as 20 intraretinal hemorrhages in each of four quadrants, definite venous beading in two or more quadrants, prominent IRMA in one or more quadrants and no signs of PDR.

Diabetic macular edema

Macular edema or retinal thickening is an important manifestation of DR and the most common cause of moderate visual loss. The intraretinal fluid comes from leaking microaneurysms or diffuses from capillary incompetence areas. Sometimes the pockets of fluid are so large that they can be seen as cystoid macular edema (CME).

Diabetic macular edema is retinal thickening within two disc diameters of the center of macula. DME patients were categorized into clinically significant macular edema (CSME) or non-CSME by ETDRS. CSME includes any one of the following lesions:

1. Retinal thickening at or within 500 microns from the center of macula.
2. Hard exudates at or within 500 microns from the center of macula associated with thickening of the adjacent retina.
3. An area or areas of retinal thickening at least one disc area in size, at least a part of which is within one disc diameter of the center of macula.

International clinical diabetic macular edema severity scale[32] has devised a simpler classification for the understanding of general ophthalmologist. The severity scale includes no DME present (no retinal thickening or hard exudates in the posterior pole), DME present (retinal thickening or hard exudates in the posterior pole). It is further classified as mild, moderate or severe depending upon the severity of macular edema.

Ancillary investigations

Diabetic retinopathy is essentially a clinical diagnosis. Slit lamp biomicroscopy, dilated fundus evaluation with a direct ophthalmoscope and indirect ophthalmoscope or contact/non-contact slit lamp biomicroscopic examination are essential in the diagnosis of DR. However, several ancillary investigations are required to aid the diagnosis, plan and execute the treatment and to document the lesions for research purposes. Stereoscopic fundus photographs may be required for research purposes and are especially useful for the assessment of macular edema.

Fundus fluorescein angiography

Fundus fluorescein angiography (FFA) is not required for identification of lesions like NVD or NVE, as these lesions are identified clinically. FFA is used to classify and treat DME into focal and diffuse variety. It also aids in diagnosis of CME. ETDRS has documented the angiographic risk factors for progression of NPDR to PDR.[33] These include widespread capillary loss, capillary dilatation and fluorescein leakage as documented on FFA. It aids in differentiating IRMAs from new vessels. IRMAs do not leak on FFA while new vessels leak profusely.

Optical coherence tomography

Optical coherence tomography (OCT) generates cross-sectional image of the retina, which is comparable to histological sections. OCT is more sensitive than clinical fundus evaluation in diagnosing CSME. OCT provides us with quantitative measurement of thickness in the posterior pole area with reasonable accuracy,[34-36] thus aiding in establishing the diagnosis of CSME.[37] The repeatability and accuracy of OCT is very helpful in assessing and prognosticating the response of CSME to any treatment.[37-39]

Diabetic macular edema is classified into different morphological patterns based on OCT.[40-42] In a study it has been shown that OCT findings correlate reasonably with FFA features.[43]

Non-mydriatic fundus photography

Digital non-mydriatic camera is being increasingly used for screening patients that can be subsequently reviewed by the experts to determine the need for referral to an ophthalmologist.

Management

Laser photocoagulation

Laser photocoagulation is indicated in CSME and in PDR with HRC.[44-46] Various factors known to worsen retinopathy may initiate treatment in severe NPDR and early PDR without HRC such as pregnancy, nephropathy, cardiac failure, coronary artery disease, cataract surgery and Yag capsulotomy, uncontrolled blood sugars, recent initiation of insulin in NIDDM patient with longstanding uncontrolled blood sugars, poor patient follow-up.[47]

Laser photocoagulation for diabetic macular edema

Diabetic macular edema is treated by coagulating microaneurysms around the fovea and applying treatment within the center of circinate rings. The ETDRS used direct focal treatment to individual microaneurysms and a grid pattern to areas of diffuse leakage and capillary non-perfusion as identified on FFA.[48] Modified grid patterns of laser treatment either alone or in combination with focal treatment have been described. Adequate treatment of DME can be achieved without FFA.[49] However, a projected angiogram during laser photocoagulation may improve the precision of treatment.[50] ETDRS demonstrated that treatment prevented moderate visual loss (loss of 15 letters or three lines on the standard ETDRS visual acuity chart) in 24% eyes, compared to 12% in untreated controls, at 3 years.[30,46,51] Residual macular edema may be re-treated 4-6 months after the initial treatment.

Laser photocoagulation for proliferative diabetic retinopathy

Diabetic retinopathy study (DRS) recommended full scatter technique to HRC eyes.[46] Panretinal photocoagulation (PRP) can cause macular edema or lead to worsening of existing edema, hence macular edema is treated prior to commencement of panretinal treatment.[52-54]

The DRS found that PRP prevented severe visual loss by over 50% at 2 and 4 years of follow-up.[45,46] When eyes with high-risk factors were considered, severe visual loss was found in 11% treated eyes and in 26% untreated controls. The visual benefit was apparent from 16 months of the study, lasted throughout the study period and was sustained for several years after the study.

Additional treatment is performed when there is residual neovascularization and areas of skipped treatment after PRP. Burns are placed over skipped areas, between previous laser scars, more centrally towards the optic disc and macula and in areas of neovascularization.[55]

The argon green (514 nm), frequency doubled Nd:YAG (532 nm), krypton red (647 nm), diode (810 nm) and tunable dye (560-640 nm) lasers are all reported to be effective in the treatment of DR. The choice of wavelength is not critical from a clinical point of view and does not have a major effect on the visual outcome.[56] Focal laser treatment with light laser photocoagulation and subthreshold micropulse diode laser are also emerging.[57] A new type of scanning laser such as patterned scanning laser photocoagulation (PASCAL) has been described, which is capable of giving multiple spots with a single foot pedal depression.[58]

Pars plana vitreous surgery in diabetic retinopathy

Pars plana vitrectomy (PPV) has been used extensively to treat various complications of DR. The major indications are non-clearing vitreous hemorrhage, macula-involving or macula-threatening tractional retinal detachment and combined tractional-rhegmatogenous detachment.[59] Less common indications are macular edema with a thickened and taut posterior hyaloid, macular heterotropia, epiretinal membrane, severe premacular hemorrhage, neovascular glaucoma with cloudy media[59] and ghost cell glaucoma.[60]

Diabetic retinopathy vitrectomy study (DRVS) randomized 370 eyes with extensive neovascularization and visual acuity of 20/400 or better into two groups of early vitrectomy or observation alone.[61] The results indicate that such patients probably do not benefit from early vitrectomy. They should be observed closely so that vitrectomy, when needed, can be undertaken promptly. DRVS[62] also studied diabetic eyes with vitreous hemorrhage and visual acuity less than 5/200 for 6 months and randomized these into two groups of those who received immediate surgery and those whose surgery was deferred for another 6 months. The study recommended early surgery in type 1 diabetic patients, more so in bilateral cases and one-eyed patients. It is important to note that DRVS noticed loss of light perception (approximately 25%) who received immediate vitrectomy.

Over the course of time, with the improvement in instruments and surgical techniques, the spectrum of indications for vitrectomy has been extended to include recalcitrant DME with or without taut posterior hyaloid membrane.[59] Vitrectomy was found to be useful in eyes with diffuse macular edema with vitreomacular traction due to taut posterior hyaloid membrane.[63] The removal of various local growth factors, such as VEGF, angiotensin and inflammatory cytokines (IL-6)[64,65] in vitreous surgery, helps to retard progression of DME. Ikeda *et al*.[66] suggested that the removal of the barrier between vitreous cavity and retina might lead to improved fluid diffusion from the retinal tissue. Various studies suggest that the presence of tangential vitreomacular tractional forces combined with the local presence of a number of cytokines and growth factors contributes to the development of DME and removal of these benefited macular edema.[67-71] Various studies have reported better outcome in DME when peeling of internal limiting membrane (ILM) is combined with PPV.[72-73] Removal of massive hard exudates with PPV from the fovea has lead to mixed response in terms of improvement of vision in low-vision patients[74-75] [Figures 1 and 2].

Newer strategies in diabetic retinopathy management

Systemic control

DCCT[18] showed that in intensively treated group, the risk of onset of retinopathy was reduced by 76%, risk of progression of retinopathy by 63%, risk of development of CSME by 23% and the need for laser treatment by 56% compared to the conventional group. This benefit persisted even 4 years after initiation of intensive therapy.[76] Similar results were seen in type 2 diabetic patients by UKPDS,[77] which showed that in intensively treated group the risk of progression of retinopathy was reduced by 17%, risk of development of vitreous hemorrhage by 23%, need for laser treatment by 29% and risk of development of legal blindness by 16% compared to the conventional group. Further DCCT[78] highlighted that after initiation of intensive insulin therapy there may be an initial transient worsening, however eventually these patients fare much better in the long run. Recent studies showed the direct relation of higher levels of glycosylated hemoglobin with persistent CSME[79] and inadequate response of PDR to PRP.[80]

The WESDR found a 17% prevalence of hypertension at baseline and a 25% incidence after 10 years in type 1 diabetics.[81] UKPDS[82] showed that in intensive blood pressure control group, there was a 34% ($P = 0.0004$) and 47% ($P = 0.004$) reduction in risk of DR progression and moderate visual acuity loss, respectively, compared to the control group after a median follow-up of 8.4 years.

Anemia has been found to be an independent risk factor for the development of high-risk proliferative PDR.[83,84] Beneficial effect of anemia treatment in patients of DR has been documented.[24,85,86]

ETDRS[87] identified elevated levels of serum cholesterol and low-density lipoproteins (LDL) as independent risk factors for the development of hard exudates, which is a major risk factor leading to subfoveal fibrosis. The beneficial role of statins such as atorvastatin (HMG-CoA reductase inhibitor) as an adjunct to standard treatment in patients with DME has been documented.[22]

Various cross-sectional and longitudinal studies have reported a relationship between proteinuria and retinopathy.[88-89] The presence and severity of DR is an indicator of the risk of gross proteinuria and conversely, proteinuria predicts

presence of PDR. A beneficial effect of ACE inhibitors and angiotensin receptor antagonists on both proteinuria (micro- or macroalbuminuria) and retinopathy, even in normotensive patients, has been shown.[90,91] A few studies have reported a beneficial effect of dialysis and renal transplant on DR with improved stabilization and response of retinopathy to laser treatment.[92,93]

In a small pilot study, it has been shown that optimal metabolic control of all the above factors led to a significant reduction in macular thickness and a trend towards visual improvement after 6 weeks even without focal laser photocoagulation.[94]

Pharmacotherapy

Pharmacological agents can affect the metabolic pathway at various levels so that the diabetes complications such as retinopathy, neuropathy and nephropathy can be prevented. Most of the diabetes-related complications, such as macular edema and neovascularization, occur secondary to the release of the growth factors in response to retinal ischemia from alterations in the structure and cellular composition of the microvasculature.[95,96]

VEGF is produced by the pigment epithelial cells, pericytes and endothelial cells of the retina in response to hypoxia.[16,95] VEGF aids inflammation by inducing intracellular adhesion molecule-1 (ICAM-1) expression and leukocyte adhesion.[97] Specific inhibition of VEGF activity is able to prevent retinal neovascularization and associated blood flow abnormalities.

Corticosteroids have been demonstrated to inhibit the expression of the VEGF gene. Nauck *et al*.[98] demonstrated that corticosteroids abolished the induction of VEGF by the pro-inflammatory mediators, such as pigment-derived growth factor (PDGF) and platelet-activating factor (PAF), in a time- and dose-dependent manner. Thus, corticosteroids downregulate VEGF production and possibly prevent breakdown of the blood-retinal barrier. Similarly, steroids have antiangiogenic properties possibly due to attenuation of the effects of VEGF. Both of these steroid effects have been utilized as intravitreal or posterior subtenon injection to cause temporary reduction of edema even prior to laser photocoagulation in DME and neovascularization in various studies[99,100] [Figures 3-6]. Intravitreal implants (Fluocinolone acetonide) may permit the drug action for longer duration.[101]

Human clinical studies on effect of intravitreal administered anti-VEGF aptamer, pegaptanib sodium (Macugen) and antibodies, ranibizumab (Leucentis) and bevacizumab (Avastin) on DME has shown favorable results.[102-105] Off-label use of intravitreal anti-VEGF drug bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA) has been shown to be useful in causing regression of neovascularization in PDR[106,107] [Figures 7-9]. It has also been used as a preoperative adjunct to calm down the fibrovascular proliferation before vitrectomy.[108]

Protein kinase C (PKC) beta has an important role in regulating endothelial cell permeability[109] and is an important signaling component for VEGF.[110] The orally administered PKC-β isoform-selective inhibitor ruboxistaurin (RBX) in subjects with moderately severe to very severe NPDR was well-tolerated and reduced the risk of visual loss but did not prevent DR progression.[111] RBX treatment was associated with a reduction of retinal vascular leakage in eyes with DME.[112]

Aldose reductase plays an important role in polyol pathway, which generates sorbitol during hyperglycemia. Sorbitol accumulation, in turn, disrupts the osmotic balance, thus destroying the retinal cells such as pericytes.[113] Aldose reductase inhibitors (ARI), such as sorbinil, ponalrestat and tolrestat, have shown decrease in capillary cell death, microaneurysm count and fluorescein leakage.[114-117] However, clinical trials of ARI had little therapeutic success.

Trials with long acting octreotide (a somatostatin analog and growth hormone/IGF-1 antagonist) (Sandostatin; Novartis, AG, Basel, Switzerland) delayed the time to progression of retinopathy, but had no effect on visual acuity or progression to macular edema.[118]

Cyclooxygenase (COX)-2 enzymes cause angiogenesis through prostanoid, which stimulates expression of VEGF and subsequently endothelial cell proliferation. COX-2 inhibitors (APHS and etodolac) have shown prevention of neovascularization in experimental conditions.[119] Human trials evaluating effects of the COX-2 inhibitor, celecoxib, are still underway. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), apart from the hypotensive effects, stimulate both VEGF and corresponding receptor expression. In experimental models, ACE inhibitors have been shown to inhibit VEGF expression. Clinically, the results of ACE inhibitors are variable.[120,121] Among ARBs, in a small study, losartan was shown to have no beneficial effect on DME.[122]

Screening for Diabetic Retinopathy

Ophthalmoscopy

Ophthalmoscopy is the most commonly used technique to screen for DR. When performed by an ophthalmologist, the specificity of direct and indirect ophthalmoscopy was high, but the sensitivity was low (34-50%), particularly for early retinopathy, in comparison to 7-field stereo photographic assessment.[123]

Digital imaging

Digital imaging makes fundus photography easier and more widely accessible. It may be used to obtain fundus images through non-dilated pupils. Mydriasis is usually necessary in older patients. Single-field fundus photography with interpretation by trained readers could serve as a screening tool to identify patients with DR.[124]

Telemedical screening

A major advantage of digital technologies is the ability to transmit images to a centralized reading center for grading. The Joslin Diabetes Center in Boston has developed the Joslin Vision Network (JVN), which includes a remote imaging system, a centralized grading center and a data storage system. Implementing retinal imaging technology in a primary care setting results in a significant increase in the rate of DR surveillance and in the rate of laser treatment for DR.

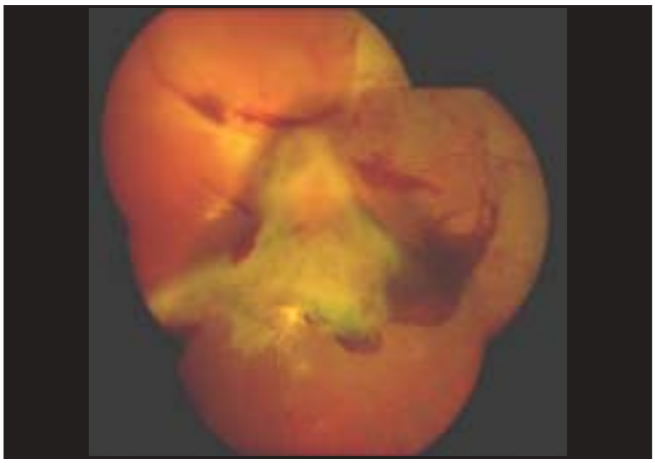

Figure 1: Case 1: Fundus photograph of the right eye showing massive peripapillary brovascular proliferation with vitreous hemorrhage

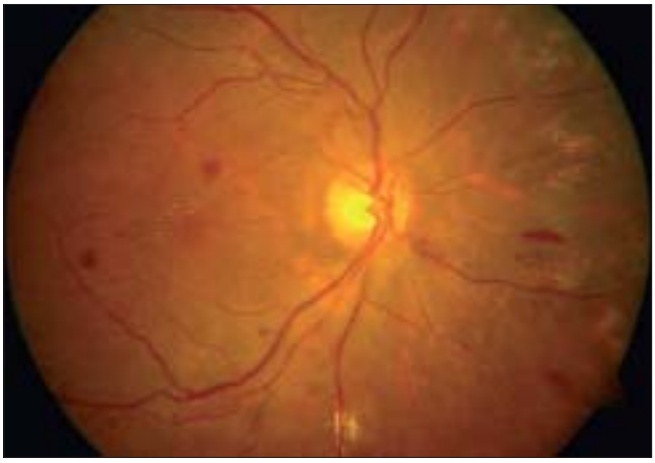

Figure 2: Case 1: Fundus photograph of the same eye after pars plana vitreous surgery

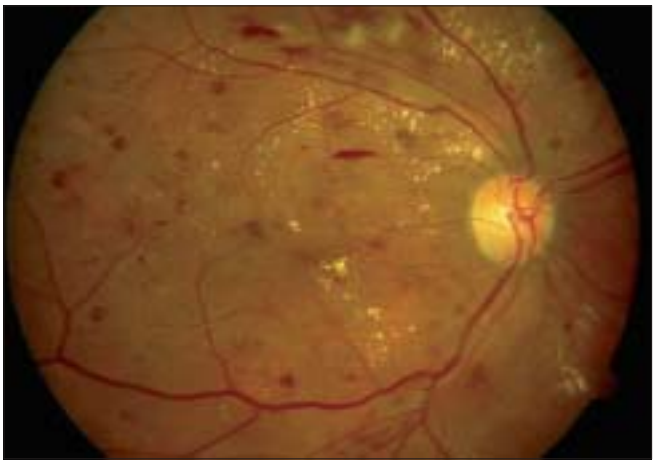

Figure 3: Case 2: Fundus photograph of the right eye shows severe non-proliferative diabetic retinopathy with macular edema and hard exudates threatening the foveal center

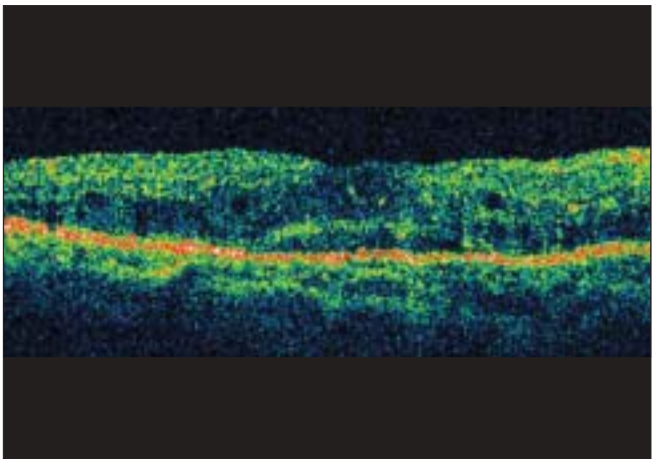

Figure 4: Case 2: Optical coherence tomography line scan shows retinal thickening with spongy retina and cystoid changes in the center along with subfoveal serous detachment

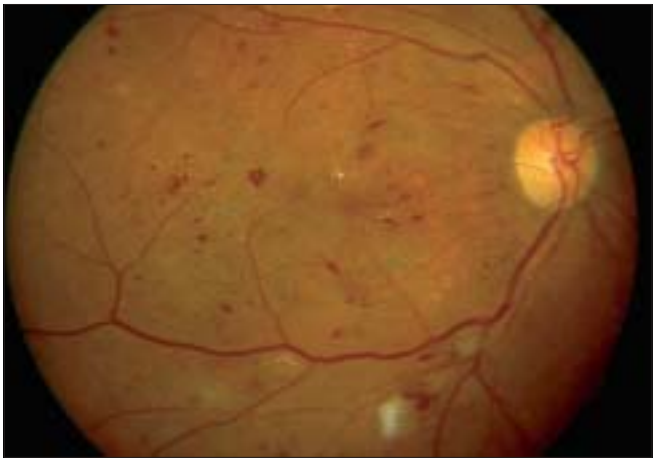

Figure 5: Case 2: Patient underwent grid laser photocoagulation 2 weeks after receiving 40-mg subtenon triamcinolone injection. Three months post-laser treatment, fundus photograph of the same eye shows severe non-proliferative diabetic retinopathy without signi cant macular edema

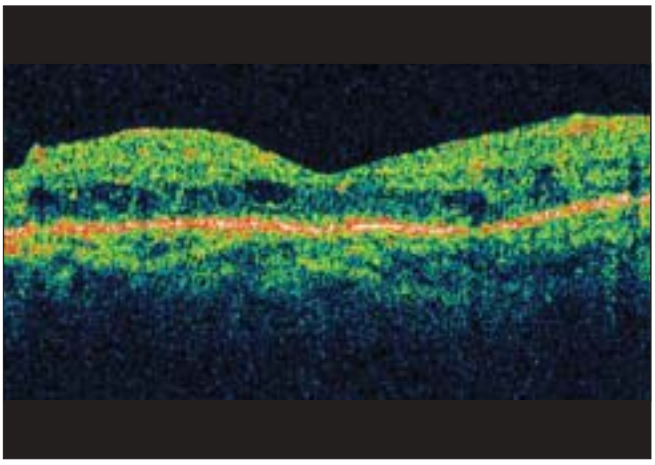

Figure 6: Case 2: Three months post-laser treatment, optical coherence tomography line scan shows mild retinal thickening with spongy retina

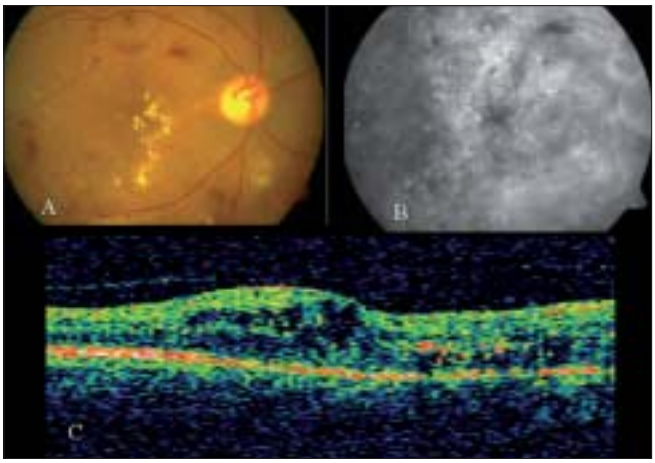

Figure 7: Case 3: Fundus photograph of the right eye shows severe non-proliferative diabetic retinopathy with macular edema (a). Late phase of angiogram shows early microaneurysmal leakage with diffuse late leakage with cystoid changes (b). Optical coherence tomography line scan shows retinal thickening with spongy retina with cystoid changes in the center (c)

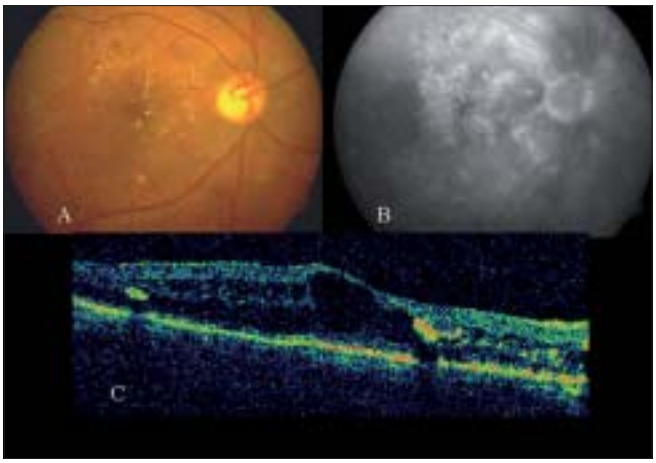

Figure 9: Case 3: Ten weeks after Avastin, fundus photograph of the same eye shows reappearance of macular edema (a). Late phase of angiogram shows reappearance of diffuse leakage at 10 weeks after Avastin (b). Optical coherence tomography line scan at 10 weeks after Avastin shows increase in retinal thickening, showing that the effect of anti-VEGF drugs Avastin is transient (c)

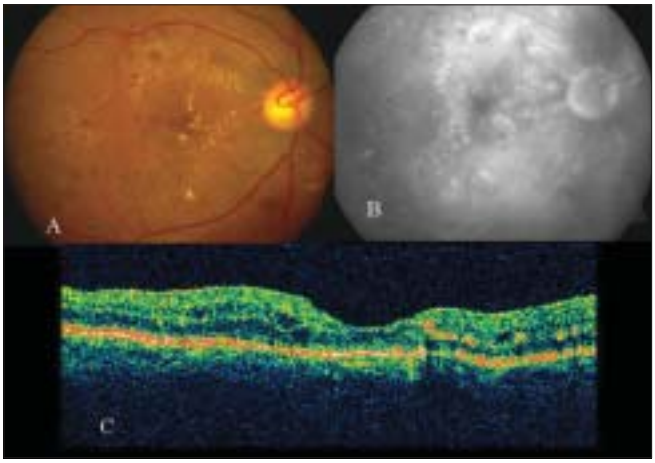

Figure 8: Case 3: Fundus photograph of the same eye six weeks after receiving 1.25 mg/0.05 ml intravitreal Avastin shows decreased macular edema (a). Late phase of angiogram shows reduction in diffuse leakage 6 weeks after Avastin (b). Optical coherence tomography line scan shows marked reduction in retinal thickening and restoration of foveal contour at 6 weeks after Avastin (c)

Conclusions

There were 31.7 million diabetics in India in year 2000 with a projection to reach 79.4 million by year 2030. Developing strategies for screening of population for early detection of DR is engaging attention of several groups in India. The present review outlines the magnitude of the problem in India, conventional and current strategies to manage the potentially blinding complications of DM. While laser photocoagulation and pars plana vitreous surgery remain the standards of care, recent successful use of several molecules is bringing about a paradigm shift in favor of pharmacotherapy. The ophthalmologists should encourage a good comprehensive systemic control for better outcomes.

References

1. National society to prevent blindness. In: Visual problems in the US data analysis definition, data sources, detailed data tables, analysis, interpretation. New York: National society to prevent blindness; 1980; 1-46.
2. Williams R, Airey M, Baxter H. Epidemiology of diabetic retinopathy and macular edema: A systematic review. Eye 2004;18:963-83.
3. Malone JI, Morrison AD, Pavan PR, Cuthbertson DD. Diabetic Control and Complications Trial: Prevalence and significance of retinopathy in subjects with type 1 diabetes of less than 5 years duration screened for the diabetes control and complications trial. Diabetes Care 200;124:522-6.
4. Kohner EM, Aldington SJ, Stratton IM. United Kingdom Prospective Diabetes Study, 30: Diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. Arch Ophthalmol 1998;116:297-303.
5. 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.
6. Sharma RA. Diabetic eye disease in southern India. Community Eye Health 1996;9:56-8.
7. Wild S, Roglic G, Green A. Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-53.
8. Dandona L, Dandona R, Naduvilath TJ. Population based assessment of diabetic retinopathy in an urban population in southern India. Br J Ophthalmol 1999;83:937-40.
9. Rema M, Premkumar S, Anitha B. Prevalence of diabetic retinopathy in urban India: The Chennai Urban Rural Epidemiology Study (CURES) eye study. Invest Ophthalmol Vis Sci 2005;46:2328-33.
10. Klein R, Klein BEK, Moss SE. Visual impairment in diabetes. Ophthalmology 1984;91:1-9.
11. Moss SE, Klein R, Klein BE. Ten-year incidence of visual loss in a diabetic population. Ophthalmology 1994;101:1061-70.
12. Kubawara T, Cogan DG. Retinal vascular patterns VI: Mural cells of the retinal capillaries. Arch Ophthalmol 1962;69:492-502.

13. Williamson JR, Kilo C. Extracellular matrix changes in diabetes mellitus. In: Comparative pathobiology of major age-related diseases. Scarpelli DG, Migahi DG, editors. New York: Liss; 1984. p. 269-88.
14. Ferris FL III, Patz A. Macular edema: A complication of diabetic retinopathy. Surv Ophthalmol 1984;28:452-61.
15. Miyamoto K, Khosrof S, Bursell SE. Prevention of leukostasis and vascular change in streptozotocin induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. Proc Natl Acad Sci USA 1999;96:10836-41.
16. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, *et al*. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480-7.
17. Klein R, Klein BE, Moss SE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, II: Prevalence and high risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1984;102:520-6.
18. The Diabetes Control and Complications Trial 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.
19. EDIC research group. Retinopathy and nephropathy in type 1 diabetes patients four years after trial of intensive therapy. N Engl J Med 2000;342:381-9.
20. Mathiesen ER, Ronn B, Storm B. The natural course of microalbuminuria in insulin-dependent diabetes: A 10-year prospective study. Diabetes Med 1995;12:482-7.
21. Diabetes Control and Complications Trial Research Group. Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. Diabetes 1997;46: 1829-39.
22. Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. Am J Ophthalmol 2004;137:675-82.
23. Davis MD, Fisher MR, Gangnon RE. 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.
24. Singh R, Gupta V, Gupta A, Bhansali A. Spontaneous closure of microaneurysms in diabetic retinopathy with treatment of co-existing anemia. Br J Ophthalmol 2005;89:248-9.
25. Klein BE, Moss SE, Klein R. Is menarche associated with diabetic retinopathy? Diabetes Care 1990;13:1034-8.
26. Klein R, Klein BE, Jensen SC, Moss SE. The relation of socioeconomic factors to the incidence of proliferative diabetic retinopathy and loss of vision. Ophthalmology 1994;101:68-76.
27. Klein BE, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. Diabetes Care 1990;13:34-40.
28. Horvat M, Maclean H, Goldberg L, Crock GW. Diabetic retinopathy in pregnancy: A 12-year prospective survey. Br J Ophthalmol 1980;64:398-403.
29. Moloney JB, Drury MI. The effect of pregnancy in the natural course of diabetic retinopathy. Am J Ophthalmol 1982;93:745-56.
30. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report no 9. Ophthalmology 1991;98:766-85.
31. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy: ETDRS report number 12. Ophthalmology 1991;98:823-33.
32. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CA, Davis M, *et al*. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677-82.
33. Early Treatment Diabetic Retinopathy Study Research Group. Fluorescein angiographic risk factors for progression of diabetic retinopathy: ETDRS report number 13. Ophthalmology 1991;98: 834-40.
34. Sadda SR, Wu Z, Walsh AC, Richine L, Dougall J, Cortez R, *et al*. Errors in retinal thickness measurements obtained by optical coherence tomography. Ophthalmology 2006;113:285-93.
35. Polito A, Del Borrello M, Polini G, Furlan F, Isola M, Bandello F. Diurnal variation in clinically significant diabetic macular edema measured by the Stratus OCT. Retina 2006;26:14-20.
36. Goebel W, Franke R. Retinal thickness in diabetic retinopathy: Comparison of optical coherence tomography, the retinal thickness analyzer and fundus photography. Retina 2006;26:49-57.
37. Panozzo G, Gusson E, Parolini B, Mercanti A. Role of OCT in the diagnosis and follow up of diabetic macular edema. Semin Ophthalmol 2003;18:74-81.
38. Luttrull JK, Spink CJ. Serial optical coherence tomography of sub threshold diode laser micro pulse photocoagulation for diabetic macular edema. Ophthalmic Surg Lasers Imaging 2006;37: 370-7.
39. Patel JI, Hykin PG, Schadt M, Luong V, Fitzke F, Gregor ZJ. Pars plana vitrectomy for diabetic macular edema: OCT and functional correlations. Eye 2006;20:674-80.
40. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. Am J Ophthalmol 1999;127:688-93.
41. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. Am J Ophthalmol 2006;142: 405-12.
42. Panozzo G, Parolini B, Gusson E, Mercanti A, Pinackatt S, Bertoldo G, *et al*. Diabetic macular edema: An OCT-based classification. Semin Ophthalmol 2004;19:13-20.
43. Kang SW, Park CY, Ham DI. The correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema. Am J Ophthalmol 2004;137:313-22.
44. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: ETDRS Report Number 1. Arch Ophthalmol 1985;103:1796-806.
45. Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 1976;81: 383-96.
46. Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: Clinical application of the Diabetic Retinopathy Study (DRS) findings: DRS Report Number 8. Ophthalmology 1981;88:583-600.
47. Davis MD. Proliferative diabetic retinopathy. In: Ryan SJ, Schachat AP, Murphy RB, editors. Vol 2, Retina St. Louis: CV Mosby Co; 1994. p. 1320-59.
48. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: ETDRS Report Number 2. Ophthalmology 1987;94:761-74.
49. Abu el Asrar, Morse PH. Laser photocoagulation control of diabetic macular edema without fluorescein angiography. Br J Ophthalmol 1991;75:97-9.
50. Kylstra JA, Brown JC, Jaffe GJ. The importance of fluorescein angiography in planning laser treatment of diabetic macular edema. Ophthalmology 1999;106:2068-73.
51. Early Treatment Diabetic Retinopathy Study Research Group. ETDRS Report Number 4. Int Ophthalmol Clin 1987;27:265-72.
52. Early Treatment Diabetic Retinopathy Study Research Group. Techniques for scatter and local photocoagulation treatment of

diabetic retinopathy: ETDRS Report Number 3. Int Ophthalmol Clin 1987;27:254-64.

53. Diabetic Retinopathy Study Research Group. Macular edema in Diabetic Retinopathy Study (DRS) patients: DRS Report Number 12. Ophthalmology 1987;94:754-60.
54. Diabetic Retinopathy Study Research Group. Factors influencing the development of visual loss in advanced diabetic retinopathy: DRS Report Number 10. Invest Ophthalmol Vis Sci 1985;26:983-91.
55. Diabetic Retinopathy Study Research Group. Photocoagulating treatment of Proliferative diabetic retinopathy: A short report of long-range results. DRS report number 4. In: Proceeding of the 10th Congress of the international diabetes federation. Amsterdam: Excerpta Medica; 1980.
56. Bressler SB. Does wavelength matter when photocoagulating eyes with macular degeneration or diabetic retinopathy. Arch Ophthalmol 1993;111:177-80.
57. Bandello F, Pognuz R, Polito A, Pirracchio A. Diabetic macular edema: Classification, medical and laser therapy. Semin Ophthalmol 2003;18:251-8.
58. Blumenkranz MS, Yellachich D, Andersen DE, Wiltberger MW, Mordaunt D. Semi automated patterned scanning laser for retinal photocoagulation. Retina 2006;26:370-6.
59. Rosenblatt BJ, Benson WE. Diabetic retinopathy. In: Yanoff M, Duker JS, editors. Ophthalmology. 2nd ed. vol 2, p. 877-86.
60. Spraul CN, Grossniklais HE. Vitreous hemorrhage. Surv Ophthalmol 1997;42:3-39.
61. Diabetic retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision: Results of a randomized trial. Diabetic retinopathy vitrectomy study report 3. Ophthalmology 1998;95:1307-20.
62. Diabetic retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy: Two-year results of a randomized trial: Diabetic retinopathy vitrectomy study report 2. Ophthalmology 1998;95:1307-20.
63. Massin P, Duguid G, Erginay A. Optical coherence tomography for evaluating diabetic macular edema before and after vitrectomy. Am J Ophthalmol 2003;135:167-77.
64. Funastu H, Yamashita H, Ikeda T. Relation of diabetic macular edema to cytokines and posterior vitreous detachment. Am J Ophthalmol 2003;135:321-7.
65. Funastu H, Yamashita H, Ikeda T. Vitreous levels of IL 6 and VGEF are related to diabetic macular edema. Ophthalmology 2003;135:1690-6.
66. Ikeda T, Sato K, Katano T, Hayashi Y. Attached posterior hyaloid membrane and the pathogenesis of honeycombed cystoids macular edema in patients with diabetes. Am J Ophthalmol 1999;127:478-9.
67. Lewis H, Abrams G, Blumenkranz M, Campo R. Vitrectomy for diabetic macular edema associated with posterior hyaloidal traction. Ophthalmology 1992;99:753-9.
68. Kent D, Vinores S, Campochiaro P. Macular edema: The role of soluble mediators. Br J Ophthalmol 2000;84:542-5.
69. Kishi S, Shimizu K. Posterior vitreous precortical pocket. Arch Ophthalmol 1990;108:979-82.
70. Pendergast SD, Hassan TS, Williams GA. Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid. Am J Ophthalmol 2000;130:178-86.
71. Tachi N, Ogino N. Vitrectomy for diffuse macular edema in cases of diabetic retinopathy. Am J Ophthalmol 1996;122:258-60.
72. Heiji EC, Hendrikse F, Kessels AG, Paul J, Derhaag FM. Vitrectomy results in diabetic macular edema without evident vitreomacular traction. Graefes Arch Clin Exp Ophthalmol 2001;239:264-70.
73. Gandofer A, Messmer E, Ulbig M, Kampik A. Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and inner limiting membrane. Retina 2000;20:126-33.
74. Takagi H, Otani A, Kiryu J, Ogura Y. New surgical approach for removing massive foveal of sub macular hard exudates in diabetic macular edema. Ophthalmology 1999;106:249-56.
75. Takaya K, Suzuki Y Mizutani H. Long-term results of vitrectomy for removal of sub macular hard exudates in patients with diabetic maculopathy. Retina 2004;24:23-9.
76. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342: 381-9.
77. 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.
78. Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol 1998;116:874-86.
79. Do DV, Shah SM, Sung JU, Haller JA, Nguyen QD. Persistent diabetic macular edema is associated with elevated hemoglobin A1c. Am J Ophthalmol 2005;139:620-3.
80. Kotoula MG, Koukoulis GN, Zintzaras E, Karabatsas CH, Chatzoulis DZ. Metabolic control of diabetes is associated with an improved response of diabetic retinopathy to panretinal photocoagulation. Diabetes Care 2005;28:2454-7.
81. Klein R, Klein BE, Lee KE. The incidence of hypertension in insulin-dependent diabetes. Arch Intern Med 1996;156:622-7.
82. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS 38. BMJ 1998;317:703-13.
83. Davis MD, Fisher MR, Gangnon RE. 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.
84. Qiao Q, Keinanen-Kiukaanniemi S, Laara E. The relationship between hemoglobin levels and diabetic retinopathy. J Clin Epidemiol 1997;50:153-8.
85. Shorb SR. Anemia and diabetic retinopathy. Am J Ophthalmol 1985;100:434-6.
86. Friedman EA, Brown CD, Berman DH. Erythropoietin in diabetic macular edema and renal insufficiency. Am J Kidney Dis 1995;26:202-8.
87. Chew EY, Klein ML, Ferris FL. 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.
88. Estacio RO, McFarling E, Biggerstaff S. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. Am J Kidney Dis 1998;31:947-53.
89. Mogensen CE, Chachati A, Christensen CK. Microalbuminuria: An early marker of renal involvement in diabetes. Uremia Invest 1985;9:85-95.
90. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus: A randomized, controlled trial. Ann Intern Med 1998;128:982-8.
91. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993;118:577-81.
92. Tokuyama T, Ikeda T, Sato K. Effects of haemodialysis on diabetic macular leakage. Br J Ophthalmol 2000;84:1397-400.

93. Pearce IA, Ilango B, Sells RA, Wong D. Stabilization of diabetic retinopathy following simultaneous pancreas and kidney transplant. Br J Ophthalmol 2000;84:736-40.

94. Singh R, Abhiramamurthy V, Gupta V, Gupta A, Bhansali A. Effect of Multifactorial Intervention on Diabetic Macular Edema. Diabetes Care 2006;29:463-4.

95. Aiello L, Avery R, Arrigg P. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Eng J Med 1994;331:1480-7.

96. Antonelli-Orlidge A, Smith S, D'Amore P. Influence of pericytes on capillary endothelial cell growth. Am Rev Respir Dis 1989;140:1129-31.

97. Ishida S, Usui T, Yamashiro K. VEGF164 is pro inflammatory in the diabetic retina. Invest Ophthalmol Vis Sci 2003;44:2155-62.

98. Nauck M, Roth M, Tamm M, Eickleberg O, Weiland H, Stulz P, *et al*. Induction of vascular endothelial growth factor by platelet-activating factor and platelet-derived growth factor is down regulated by corticosteroids. Am J Respir Cell Mol Biol 1997;16:398-406.

99. Jonas J, Degenring R. Intravitreal injection of crystalline triamcinolone acetonide in the treatment of diffuse diabetic macular edema. Klin Monatsbl Augenheikd 2002;219:429-32.

100. Martidis A, Duker J, Greenberg P. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002;109: 920-7.

101. Pearson P, Levy B, Comstock T. Fluocinolone Acetonide Implant Study Group. Fluocinolone acetonide intravitreal implant to treat diabetic macular edema: 3-year results of a multicenter clinical trial. Invest Ophthalmol Vis Sci 2006;47:1020-7.

102. Cunningham ET Jr, Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, *et al*. A phase II randomized double-masked trial of pegaptanib: An anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112:1747-57.

103. Nguyen QD, Tatlipinar S, Shah SM, Haler JA. Vascular endotherlial growth factor is a critical stimulus for diabetic macular edema. Am J Ophthamol 2006;142:961-9.

104. Chun DW, Heier JS, Topping TM, Duker JS. A pilot study of multiple intravitreal injections of ranibizumab in patients with center involving clinically significant macular edema. Ophthalmology 2006;11113:1706-12.

105. Haritoglou C, Kook D, Neubauer A, Wolf A. Intravitreal Bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina 2006;26:999-1005.

106. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. Retina 2006;26:275-8.

107. Mason JO 3rd, Nixon PA, White MF. Intravitreal injection of bevacizumab (Avastin) as adjunctive treatment of proliferative diabetic retinopathy. Am J Ophthalmol 2006;142:685-8

108. Chen C, Park CH. Use of intravitreal Bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe proliferative diabetic retinopathy. Retina 2006;26: 699-700.

109. Nagpala P, Malik AB, Vuong PT, Lum H. Protein kinase C b1 over expression augments phorbol ester-induced increase in endothelial permeability. J Cell Physiol 1996;166:249-55.

110. Xia P, Aiello LP, Ishii H, Jiang ZY, Park DJ, Robinson GS, *et al*. Characterization of vascular endothelial growth factor's effect on the activation of protein kinase C, its isoforms and endothelial cell growth. J Clin Invest 1996;98:2018-26.

111. 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.

112. Strom C, Sander B, Klemp K, Aiello LP, Lund-Anderson H, Larsen M. Effect of ruboxistaurin on blood-retinal barrier permeability in relation to severity of leakage in diabetic macular edema. Invest Ophthalmol Vis Sci 2005;46:3855-8.

113. Speiser PP, Gittelsohn AM, Patz A. Studies on diabetic retinopathy, III: Influence of diabetes on intramural pericytes. Arch Ophthalmol 1968;80:332-7.

114. Sorbinil Retinopathy Trial Research Group. A randomized trial of sorbinil: An aldose reductase inhibitor, in diabetic retinopathy. Arch Ophthalmol 1990;108:1234-44.

115. Tromp A, Hooymans JM, Barendsen BC, van Doormaal JJ. The effects of an aldose reductase inhibitor on the progression of diabetic retinopathy. Doc Ophthalmol 1991;78:153-9.

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

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

118. Grant M, Mames R, Fitzgerald C. The efficacy of octeoride in the therapy of severe nonproliferative and early proliferative diabetic retinopathy. Diabetes Care 2000;23:504-9.

119. Sennlaub F, Valamanesh F, Vezquer-tello A. COX-2 in human and experimental ischemic proliferative retinopathy. Circulation 2003;108:198-204.

120. UK prospective diabetes study group. Efficacy of atenolol and captopril in reducing risk of macro vascular and micro vascular complication in type 2 diabetes. UKPDS 39. BMJ 1998,317: 713-72.

121. Gilbert R, Kelly D, Cox A. Angiotensin converting enzyme inhibition reduces retinal over expression of VEGF and hyper permeability in experimental diabetes. Diabetologia 2000,43:1360-7.

122. Knudsen ST, Bek T Poulsen PL, Hove MN, Rehling M, Mogensen CE. Effects of losartan on diabetic maculopathy in type 2 diabetic patients: A randomized, double-masked study. J Intern Med 2003;254:147-58.

123. Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: A comparison with ophthalmoscopy and standardized mydriatic color photography. Am J Ophthalmol 2002;134:204-13.

124. Williams GA, Scott IU, Haller JA, Maguire AM, Marcus D, McDonald R. Single field fundus photography for diabetic retinopathy screening: A report by American academy of Ophthalmology. Ophthalmology 2004;111:1055-62.

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