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. 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% and 54.2% in the diabetes control and complications trial (DCCT) in IDDM and 35-39% in United Kingdom Prospective Diabetes Study (UKPDS) in NIDDM. In two studies from South India, the prevalence rates of DR in NIDDM patients were 34.1% and 37%, respectively. India has 31.7 million diabetic subjects at present as per the World Health Organization (WHO) estimates. In the Andhra Pradesh Eye Disease Study (APEDS) of self-reported diabetics, the prevalence of DR was 22.4%. 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%.

**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. 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.

**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. 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.

**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. Apart from this, thickening of the capillary basement membrane and increased deposition of extracellular matrix components contribute to the development of abnormal retinal hemodynamics. In diffuse type of diabetic macular edema (DME), breakdown of the inner blood-retinal barrier results in accumulation of extracellular fluid.

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.

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). 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.

**Glycemic control**

There is an indirect relationship between the glycemic control...
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. Intensive diabetic control leads to reduction in the development and progression of all diabetic complications.

**Age and sex**
The prevalence of DR increases with increasing age in type 1 DM but not in type 2 DM.

**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.

**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.

**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 dyslipidemia, using a lipid-lowering drug, atorvastatin, as an adjunct to macular photoagulation.

**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. Anemia-induced retinal hypoxia is speculated as cause of development of microaneurysms and other retinopathy changes.

**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. 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.

**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. The cause of acceleration of DR may be a simple reflection of long duration of diabetes 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. 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 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 at least one quadrant, or venous beading in two or more quadrants, or IRMA > standard photo 8A in at least one quadrant, definition not met for
F. High-risk PDR: Includes any of the following characteristics - NPDR. This scale is based on May - June 2008 Singh
D. Very severe NPDR: Any two or more of the changes seen are especially useful for the assessment of macular edema. fundus photographs may be required for research purposes and to document the lesions for research purposes. Stereoscopic required to aid the diagnosis, plan and execute the treatment diagnosis of DR. However, several ancillary investigations are contact slit lamp biomicroscopic examination are essential in the treatment have been described. Adequate treatment of Diabetes retinopathy is essentially a clinical diagnosis. Slit lamp biomicroscopy, dilated fundus examination 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. 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, thus aiding in establishing the diagnosis of CSME. The repeatability and accuracy of OCT is very helpful in assessing and prognosticating the response of CSME to any treatment.

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

**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 photoagulation**

Laser photoagulation is indicated in CSME and in PDR with HRC. 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.

**Laser photoagulation 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. 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. However, a projected angiogram during laser photoagulation may improve the precision of treatment. 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.

Residual macular edema may be re-treated 4-6 months after the initial treatment.
Laser photoocoagulation for proliferative diabetic retinopathy

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

The DRS found that PRP prevented severe visual loss by over 50% at 2 and 4 years of follow-up. 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.

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. Focal laser treatment with light laser photocoagulation and subthreshold micropulse diode laser are also emerging. A new type of scanning laser such as patterned scanning laser photoocoagulation (PASCAL) has been described, which is capable of giving multiple spots with a single foot pedal depression.

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. 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 and ghost cell glaucoma.

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. 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 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. Vitrectomy was found to be useful in eyes with diffuse macular edema with vitreomacular traction due to taut posterior hyaloid membrane. The removal of various local growth factors, such as VEGF, angiotensin and inflammatory cytokines (IL-6) in vitreous surgery, helps to retard progression of DME. Ikeda et al 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.

Various studies have reported better outcome in DME when peeling of internal limiting membrane (ILM) is combined with PPV. 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.

Newer strategies in diabetic retinopathy management

Systemic control

DCCT 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. Similar results were seen in type 2 diabetic patients by UKPDS 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 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 and inadequate response of PDR to PRP.

The WESDR found a 17% prevalence of hypertension at baseline and a 25% incidence after 10 years in type 1 diabetics. UKPDS 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. Beneficial effect of anemia treatment in patients of DR has been documented.

ETDRS 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.

Various cross-sectional and longitudinal studies have reported a relationship between proteinuria and retinopathy. 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. 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.

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.

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.

VEGF is produced by the pigment epithelial cells, pericytes and endothelial cells of the retina in response to hypoxia. VEGF aids inflammation by inducing intracellular adhesion molecule-1 (ICAM-1) expression and leukocyte adhesion. 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. 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 intraviteal or posterior subtenon injection to cause temporary reduction of edema even prior to laser photoagulation in DME and neovascularization in various studies.

Intravitreal implants (Fluocinolone acetonide) may permit the drug action for longer duration. 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. 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 [Figures 7-9]. It has also been used as a preoperative adjunct to calm down the fibrovascular proliferation before vitrectomy.

Protein kinase C (PKC) beta has an important role in regulating endothelial cell permeability and is an important signaling component for VEGF. The orally administered PKC-δ 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. RBX treatment was associated with a reduction of retinal vascular leakage in eyes with DME.

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. Aldose reductase inhibitors (ARI), such as sorbinil, ponalrestat and tolerstat, have shown decrease in capillary cell death, microaneurysm count and fluorescein leakage. 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.

Cyclooxygenase (COX)-2 enzymes cause angiogenesis through prostanooid, which stimulates expression of VEGF and subsequently endothelial cell proliferation. COX-2 inhibitors (APHS and etodolac) have shown prevention of neovascularization in experimental conditions. 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. Among ARBs, in a small study, losartan was shown to have no beneficial effect on DME.

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.

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.

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 significant macular edema

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

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