**Review Article**

**Diabetic Retinopathy: An Overview**

Ajay Sharma, Trishna Taye, SB Rasel

**Abstract:** Diabetic Retinopathy (DR) is the most common micro vascular complication of diabetes mellitus and a major cause of legal blindness. Both ocular & systemic factors are responsible for the pathogenesis of DR. The morbidity from DR has a great impact on the society. Early diagnosis and prompt treatment reduces the complication and economic burden. The major treatments for this condition have largely remained unchanged for long years: laser photocoagulation for proliferative diabetic retinopathy and macular edema, under guidelines of the Early Treatment Diabetic Retinopathy Study (ETDRS). However, new therapeutic strategies have appeared, which raise the prospect that the years ahead will see very significant additions to the options for treatment of diabetic retinopathy. Both corticosteroids and anti-VEGF treatments are serving as additional options in the clinical management of Diabetic Retinopathy. The emergence of anti-VEGF treatments strongly highlights the advent of rational drug therapy based on the identification of causative mechanisms and molecular targets. Though Diabetic Retinopathy is irreversible, early diagnosis & prompt treatment reduces the risk of visual loss, complications and economic burden on the society.

**Key Words:** Diabetic Retinopathy, Laser Photocoagulation, Macular oedema, Anti-VEGF

**Introduction**

Diabetes mellitus (DM) is a multi-factorial metabolic disorder characterized by altered insulin production or activity, clinically manifested as elevated blood glucose. DM can be divided into type 1 or insulin dependent DM (IDDM) and type 2 or non insulin dependent DM (NIDDM). 10% to 15% have IDDM and are generally diagnosed before 40yrs of age, but the majority have NIDDM and are generally diagnosed after 40yrs. DM causes numerous long term systemic complications that have considerable associated morbidity.

Diabetic retinopathy (DR) is a highly specific vascular complication of both type 1 and type 2 DM. The development and progression of Diabetic Retinopathy is multi factorial and depends on the duration of DM among other factors. The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease. The morbidity and suffering caused by visual loss, the economic impact from diabetic retinopathy is tremendous.

**Epidemiology**

According to the World Health Organization (WHO) the total numbers of people with diabetes were 171 million in 2000, and are projected to rise up to 366 million in 2030. 80% of people with diabetes live in low and middle income countries. India has 31.7 million diabetic subjects at present. Projected figures for 2025 are 54 million. 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) prevalence of DR was 17.6%. After 20 yrs of DM nearly all patients with IDDM and more than 60% with NIDDM have some degree of retinopathy. These figures clearly indicate the magnitude of problem.

**Risk factors for DR:** The following are the risk factors which can aggravate DR.

- **Duration of Diabetes:** Duration of diabetes is a major risk factor associated with development of DR. After 5 yrs, 25% of type -1 DM patients have some form of Diabetic Retinopathy, after 10 yrs, 60% and after 15 yrs 80% have DR.

- **Hypertension:** Studies, such as The Wisconsin Epidemiological study of Diabetic Retinopathy (WESDR) and UK Prospective Diabetes study (UKPDS), suggest that
hypertension increases the risk and progression of DR and Diabetic Macular Oedema (DME). Intensive management of HTN has been demonstrated to slow retinopathy progression.7,8

♦ 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 micro albuminuria.9

♦ Serum lipid: 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 sub-foveal lipid migration in patients with type 2 diabetes and dyslipidaemia, using a lipid-lowering drug, atorvastatin, as an adjunct to macular photocoagulation10.

♦ 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 pregnancy11.

♦ Other risk factors include anemia, smoking, cataract surgery, obesity, cardiovascular disorder etc.

PATHOPHYSIOLOGY:

DR is predominantly a micro-angiopathy in which small blood vessels are particularly vulnerable to damage from hyperglycemia. Direct hyperglycemic effects on retinal cells are also likely to play a role.

Various studies have shown that chronic hyperglycemia, hypertension and hyperlipidemia contribute to the pathogenesis of DR. Hyperglycemia damages retinal vasculature in several ways and progression of DR is generally related to the severity and duration of hyperglycemia. The exact mechanism by which raised glucose levels lead to vascular disruption seen in retinopathy is poorly defined. However, various biochemical pathways have been suggested to demonstrate correlation between hyperglycemia and micro-vascular complications of retinopathy. Among these pathways, increased activity of protein kinase C (PKC) and glycation of key proteins that lead to formation of advanced glycation end products (AGEs) are more important than polyol accumulation, oxidative stress, growth factor etc.

Six basic patho-physiologic processes are recognized in the development of lesions of DR.

1. Loss of pericyte functions of retinal capillaries.
2. Out pouching of capillary walls to form micro aneurysms
3. Closure of capillaries and arterioles
4. Breakdown of blood/retinal barrier
5. Proliferation of new vessels and fibrous tissue.
6. Contraction of vitreous and fibrous proliferation with subsequent vitreous hemorrhage and retinal detachment due to traction.

DIAGNOSIS

The initial examination for a patient with diabetes includes all features of the comprehensive adult medical eye examination with particular attention to those aspects relevant to DR.

HISTORY: An initial history should consist of the following elements:

♦ Complaints (ocular and systemic) • Duration of diabetes4,6, Past glycaemic control (hemoglobin A1c)4 and medication.
♦ Medical history; eg.: Obesity, renaldisease4, hypertention4, serum lipids, pregnancy, past treatment.

EXAMINATION:

The initial examination should include the following elements:

♦ Visual acuity • Slit lamp biomicroscopy
♦ Intraocular pressure • Dilated fundoscopy including stereoscopic examination of the posterior pole
♦ For evidence of macular oedema

EXAMINATION SCHEDULE: Depends upon type of DM

1. Type 1 DM: Many studies of patients with type 1 DM reported a direct relationship between the prevalence and severity of DM and duration of diabetes.12 The development of vision threatening retinopathy is rare in children before puberty. Among the patients with type 1 DM, substantial retinopathy may develop as early as 6-7 years after onset of disease4. Ophthalmic examination should be performed beginning 3-5 years after diagnosis of type 1 DM4.

2. Type 2 DM: The time of onset of type 2 DM is often difficult to determine and may precede the diagnosis by number of years. 3% of patients whose diabetes is first diagnosed at age 30 or later will have CSME or high risk characteristics at the time of initial diagnosis of diabetes4. Ophthalmic examination should be performed once at the time of diagnosis of type 2 DM.
3. DIABETES ASSOCIATED WITH PREGNANCY:
DR can worsen during pregnancy due to metabolic changes. Patients with DM who become pregnant should be encouraged to have their eyes examined prior to conception, and during early pregnancy, should be counseled on the risk of development and progression of DR, and should be counselled to make every attempt to lower their blood glucose level to as near normal as possible for their own health and the health of the fetus. Woman who developed gestational DM do not require eye examination during pregnancy, because such individual are not at increased risk for DR during pregnancy.

Table 1- Follow up schedule:

<table>
<thead>
<tr>
<th>Diabetic type</th>
<th>Recommended time of first Examination</th>
<th>Recommended follow up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>3-5 yrs after diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Type 2</td>
<td>At the diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Prior to pregnancy type 1/2</td>
<td>Prior to conception &amp; early in the first trimester</td>
<td>No retinopathy to mild or moderate NPDR;Every 3-12 months, severe NPDR or worse;every 1-3 months</td>
</tr>
</tbody>
</table>

*Abnormal findings may dictate more frequent follow up examination

**CLINICAL FEATURES:**

**Symptoms:**
In the initial stages of diabetic retinopathy, patients are generally asymptomatic; in more advanced stages, patients may experience symptoms of floaters, blurred vision and progressive or sudden visual loss.

**SIGNS:**

*Micro aneurysm:* The earliest clinical sign of DR is a micro-aneurysm. They are located in the inner nuclear layer of the retina and appear as red dots.

*Intra retinal hemorrhage:* Dot blot hemorrhages are located in the middle layers of the retina. Flame shaped hemorrhages are located in the nerve fiber layers and follow their course.

*Hard Exudates:* They are yellow waxy appearance mainly located at the posterior pole

*Cotton-wool spots:* They result from nerve fiber layer infarctions from occlusion of pre-capillary arterioles. They are frequently bordered by micro-aneurysms and vascular hyper permeability.

*Retinal oedema:* It is characterized by retinal thickening which obscures the underlying RPE.

*Intra retinal micro vascular abnormalities (IRMA):* They are either new vessel growth within the retina or, more likely, pre-existing vessels that become shunts through areas of non perfusion.

**Venous caliber abnormality:** They are indicators of severe retinal ischemia. They can be venous dilatation, beading, loop formation.

**Neovascularization:** May be on the disc (NVD), or elsewhere on the retina(NVE).

**Pre-retinal hemorrhages and vitreous hemorrhage:**
Appear as pockets of blood within the potential space between the retina and the posterior hyaloid phase. As blood pools within this space, the hemorrhages may appear boat shaped. Vitreous hemorrhage may appear as diffuse haze or clump in the Vitreous gel.

**Fibrovascular tissue proliferation and Traction retinal detachments**

**DIABETIC MACULOPATHY:** Maculopathy is a disease of macula and can accompany any stage of DR including background retinopathy. Maculopathy is a serious condition and may affect central vision. It is characterized by macular edema and ischemic Maculopathy. Macular edema is due to extravasations of plasma proteins due to damage of blood-retinal barrier. Ischemic Maculopathy arises due to extensive micro vascular occlusion and may cause severe loss of central vision.

Diabetic Maculopathy is of the following types:
Table 2- Classification of Diabetic Retinopathy (From ETDRS)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Lesion Present</th>
</tr>
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<tbody>
<tr>
<td>Non Proliferative</td>
<td></td>
</tr>
<tr>
<td>No Diabetic Retinopathy</td>
<td>No retinal lesion</td>
</tr>
<tr>
<td>Microaneurysms only</td>
<td>No lesions other than microaneurysms</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>Microaneurysms plus retinal hemorrhages, hard exudates</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>Mild NPDR plus cotton-wool spots and/or IRMA</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>Presence of one of the following features: microaneurysms plus venous beading and/or H/MA standard photograph 2A in four quadrants, or marked venous beading in two or more quadrants or moderate IRMA (standard photograph 8A) in one or more quadrants)</td>
</tr>
<tr>
<td>Very severe NPDR</td>
<td>Two or more of the above features described in severe NPDR</td>
</tr>
<tr>
<td>Proliferative</td>
<td></td>
</tr>
<tr>
<td>PDR without HRC</td>
<td>New vessels and/or fibrous proliferations; or preretinal and/or vitreous hemorrhage</td>
</tr>
<tr>
<td>PDR with HRC</td>
<td>NVD standard photograph 10A; or less extensive NVD, if vitreous or preretinal hemorrhage is present; or NVE half disc area, if vitreous or preretinal hemorrhage is present</td>
</tr>
<tr>
<td>Advanced PDR</td>
<td>Extensive vitreous hemorrhage precluding grading, retinal detachment involving macula, or phthisis bulbi or enucleation secondary to a complication of diabetic retinopathy.</td>
</tr>
</tbody>
</table>

2. Ischemic, with or without associated CSME
3. Cystoid macular edema
4. Non-CSME

CLINICALLY SIGNIFICANT DIABETIC MACULAR OEDEMA (CSME): (figure 1)

The following are the criteria for CSME
1. Thickening of the retina located at or within 500microns from the center of the macula or
2. Hard exudates with thickening of the adjacent retina located at or within 500microns from the center of the macula or
3. A zone of retinal thickening, 1 disc area or larger in size located at or within one disc area from the center of the macula.

INVESTIGATIONS

Diabetic retinopathy is essentially a clinical diagnosis. Investigations are required to aid the diagnosis, plan and execute the treatment and document for review and research purposes.

![Fig 1: Severe NPDR: Retinal hemorrhages (red arrow) seen extensively in all four quadrants. Dilated veins indicating ischemia (Blue arrow). Also note hard exudates (yellow arrow).](image)

Fundus fluorescein angiography

ETDRS has documented the angiographic risk factors for progression of NPDR to PDR. FFA is used to classify and treat DME into focal and diffuse variety and it also aids in the diagnosis of CME.
**Optical coherence tomography (OCT)**

OCT generates cross-sectional image which provides us with quantitative measurement of thickness in the posterior pole area with reasonable accuracy, thus aiding in establishing the diagnosis of CSME. Some important features of Diabetic retinopathy are depicted in figures 2 to 4.

Management of DR:

The management of DR can be broadly classified into
1. Control of risk factors
2. Specific treatment

**CONTROL OF RISK FACTORS**

Although specific treatment modalities for retinopathy threatening vision have improved over years of clinical and research experience, importance of preventive measures (Good glycemic and blood pressure control, smoking cessation, regular eye screening) cannot be underestimated

**Specific treatment:** According to ETDRS

**Normal or minimal NPDR:** The patient with no DR or minimal NPDR (e.g. with rare microaneurysms) should be re-examined annually, because within one year only 5% to 10% of them will develop DR. Existing retinopathy will worsen by a similar percentage. Laser, colour fundus or angiography are not indicated.

**Mild to moderate NPDR without macular edema (figure 5):** Patients with mild to moderate NPDR should have a repeat examination within 6-12 months; because lesion progression is common. Laser, surgery and FFA are not indicated for this group of patients. Color fundus photo may occasionally be helpful as a baseline for future comparison and documentation.

**Fig.2:** CME: OCT showing Cystoid macular edema with elevation of retinal sensory layers (white arrow) and cystic spaces (yellow arrow)

**Fig.3:** OCT showing epiretinal membrane (white arrows)

**Fig.4:** OCT showing macular edema with pigment epithelial detachment (white arrow).

**Fig.5:** PDR with CSME: Hard exudates (yellow arrow) with retinal thickening seen within 500 microns from the foveal center, indicating CSME. Fibro-Vascular proliferation (Red arrow) can be seen along the superior temporal arcade.
For patients of mild NPDR, the 4 years incidence of earlier CSME or macular edema that is not clinically significant is 12%. For moderate NPDR, this risk increased to 23% for the patients of type 1 and type 2 DM. Patients with macular edema with no CSME should be rechecked within 3-4 months, because they are at risk of developing CSME.

**Mild to Moderate NPDR with CSME:** FFA should be done prior to laser surgery to identify treatable lesions and for identifying pathologic enlargement of FAZ (Foveal Avascular zone). The treatment of CSME has traditionally been laser. The ETDRS results showed that the risk of moderate visual loss is reduced by more than 50% for the patients who undergo appropriate laser surgery, when compared to untreated.

More recently data from the diabetic retinopathy clinical research network (DRCR.net) and other studies have demonstrated that intravitreal anti-VEGF agents and corticosteroids are effective treatments for CSME. The visual acuity gain and reduction in macular thickness following the administration of the combination of intravitreal Ranibizumab, with prompt or deferred laser were greater than the laser alone at 2 years of follow up. When treatment for macular edema is deferred, as may be desirable when the centre of macula is not involved or immediately threatened, the patients should be observed closely (at least every 3-4 months) for progression.

**SEVERE NPDR AND NON HIGH RISK PDR (Figure 6):** ETDRS data showed that severe NPDR and non high risk PDR have a similar clinical course and subsequent recommendation for treatment are similar. In eyes with severe NPDR, the risk of progression to proliferative disease is high. Half of severe NPDR will develop PDR within 1 year, and 15% will be developing high risk PDR. The ETDRS compared early PRP with deferral of PRP, defined as careful follow up (at 4 month interval) and prompt PRP if progression to high risk PDR occurred. When retinopathy is more severe, PRP should be considered and should not be delayed if the eye has reached the high risk proliferative stage. If laser surgery is indicated, full PRP is a proven surgical technique, and partial PRP is not recommended.

**HIGH RISK PDR (Figure 7):** The risk of severe visual loss in patient of high risk PDR can be reduced substantially by means of PRP as described in the ETDRS and DRS. Most patients of high risk PDR should receive PRP expeditiously.
Surgical management of DR

The indications for surgery are as follows
1. Persistent Vitreous hemorrhage (V.H)
2. Tractional Retinal detachment (R.D) involving macula
3. Combined tractional and Rhegmatogenous R.D
4. Dense persistent premacula, subhyaloid hemorrhage
5. Rubeosis iridis with V.H

Management of CSME:

The treatment technique is divided into two main categories:
1. Focal laser: direct treatment of fluorescein leaks
2. Grid laser: treatment of diffuse areas of leakage or non-perfused retinal thickening.

Pharmacotherapy

Pharmacological agents aim at preventing or reducing the release of growth factors in response to retinal ischemia from alterations in the structure and cellular composition of the microvasculature.

Pharmacological agents:

a. Anti VEGF:
   1. Pegaptanib sodium
   2. Bevacizumab
   3. Ranibizumab

b. Corticosteroids: Triamcinolone acetonide


Recent advances

- **Fenofibrate**: Fenofibrate is a peroxisome proliferator–activated receptor (PPAR)-á agonist indicated for the treatment of hypertriglyceridemia and mixed dyslipidemia. Fenofibrate (200 mg once daily) reduced the need of laser treatment for macular edema by 31% and for proliferative retinopathy by 30%.

- **Aflibercept**: Aflibercept is currently being used in clinical trials for both exudative Age related Macular Degeneration and DME. Aflibercept has a higher binding affinity than other anti-VEGF agents, which translates into greater activity at lower biological levels and, consequently, a longer duration of action.

- **Sustained drug delivery system**:
  1) Triamcinolone acetonide (TA) implant (I-vation).
  2) Dexamethasone intravitreal implant (Ozurdex) 0.7 mg for diabetic macular edema (DME) in pseudophakic patients or phakic patients scheduled for cataract surgery.
  3) Ocriplasmin (Jetrea; ThromboGenics, Belgium) has been approved by the FDA for the treatment of vitreomacular adhesion and has some efficacy in inducing a PVD30.

Conclusion:

Diabetic Retinopathy may be present without any symptoms. Visual loss due to Diabetic Retinopathy is usually irreversible. Moreover the awareness of Diabetic Retinopathy is low among the general public.

Patient access, careful medical and ophthalmological follow-up, and timely laser photocoagulation are fundamental to the successful elimination of blindness in people with diabetes mellitus.

Method of Literature Search

This review was written based on Medline searches with key words and References as appropriate and using articles cited in the references of journal articles.

References


27. IVA prevention of PRP induced complications in patients with severe PDR. Mason JO, Yunker JJ, McGwin Retina 2008 jul 29

28. Torello M, Costa RA-Actaophth 2008 jun; 86(4); 385-9
