**Introduction**

The word diabetes mellitus comes from Greek words “Diabetes” means “siphon” and mellitus which mean “honey tested urine”. It is a major risk factor of blindness in both developing and developed countries. It is estimated that diabetes mellitus affects 4 per cent of the world’s population, almost half of whom have some degree of diabetic retinopathy (DR) at any given time. DR occurs both in type 1 and type 2 diabetes mellitus and has been shown that nearly all type 1 and 75 per cent of type 2 diabetes will develop DR after 15 years duration of diabetes as shown in epidemiological studies. Visual disability from diabetes is a significant public health problem and if managed with timely intervention, the quality of life can be preserved. This article aims at providing an overview of proliferative diabetic retinopathy (PDR) and recent advances in the management.

**Pathogenesis and course of Proliferative Diabetic Retinopathy (PDR)**

Retinal neovascularization occurs in response to retinal ischemia. Angiogenic factors have been isolated from ocular tissues in proliferative diabetic retinopathy patients. Major factors have particular relevance in PDR: Vascular endothelial Growth factor (VEGF), basic Fibroblast Growth Factor (b-FGF) and Insulin like Growth Factor (IGF). They stimulate endothelial cell proliferation, migration and organisation into three dimensional collagen matrices to form capillary like tubes.

New vessels once formed progress along the routes of least resistance. The absence of a true internal limiting membrane on the disc explains the prevalence of new vessels at that location. Also, neovascularization seems to grow more easily on a preformed connective tissue framework. Thus, a shallow detached posterior vitreous face is a frequent site of growth of new vessels. The new vessels, initially naked, undergoes through a stage of further proliferation with connective tissue formation. The fibrous component becomes more prominent, with the fibrotic tissue being either vascular or avascular. The fibrovascular type is found in association with vessels that extend into the vitreous cavity or with abnormal new vessels on the surface of the retina or disc. The avascular variety usually results from organization or thickening of the posterior hyaloid face. These proliferations exert traction on the retina and may lead to retinal detachment. Finally, the end stage is characterized by regression of the vascular systems. No further damage may take place, but there may be contraction of the connective tissue components, development of subhyaloid bands, thickening of the posterior vitreous face, appearance of retinoschisis, retinal detachment and formation of retinal break.

**Clinical signs of PDR**

1) **Neovascularisation** - Proliferative diabetic retinopathy is characterised by new vessel growth or by fibrous tissue proliferation on optic disc, retinal vasculature elsewhere and along the partially detached posterior hyaloid. Proliferative diabetic retinopathy also includes rubeosis iridis or new vessels in the anterior chamber angle.

Severities of new vessels increases on a four step scale:
- None
- Neovascularisation elsewhere (NVE)
- Neovascularisation of disc (NVD)
- Neovascularisation of the anterior chamber angle with neovascular glaucoma (NVG)
2) Vitreous and preretinal haemorrhage - As long as the posterior hyaloid remains attached neovascular proliferation appears to be slightly anterior to retina and is usually asymptomatic. Small haemorrhages may occur at the growing tip of the new vessels, mostly remain subhyaloid. As the posterior hyaloids detaches, haemorrhages become less confined and symptoms appear. Contraction of the vitreous or fibro vascular proliferation can lead to avulsion of a retinal vessel, usually a vein and cause vitreous haemorrhage. Blood in the fluid vitreous behind the detached posterior vitreous face remains red until absorbed (over weeks to months). Haemorrhage into formed vitreous tends to turn white over time and may take several months to clear.

3) Rubeosis iridis / Neovascularisation of angle

Classification of PDR (ETDRS)
- Early PDR
  New vessels not meeting the criteria for high risk characteristic
- High risk PDR
  NVD > 1/3-½ disc area
  NVD < 1/3 disc area with vitreous or preretinal haemorrhage
  NVE > ½ disc area and preretinal or vitreous haemorrhage
If both NVD & NVE count severity of NVD

Investigations in PDR
Fundus photography
Fundus fluorescein angiography (FFA) - Helps in identifying areas of capillary nonperfusion and occult/ invisible NVE if present. Areas of macular leak in FFA have to be treated prior to PRP as laser may worsen the edema. If associated with ischemic maculopathy the visual prognosis is generally poor. Fluorescein angiography also aids in the follow-up and evaluation of treatment.

Fig 2 Neovascularisation elsewhere in retina (NVE) with FFA picture showing leaks with Capillary non perfusion areas.

Fig 3 A and B- showing the advantage of FFA in picking up occult NVE

Fig 4 A- vitreous haemorrhage in PDR, B – Bscan showing diabetic tractional retinal detachment.

Fig 5 Showing active new vessels 1 year after laser photocoagulation requiring additional laser treatment.

Fig 6 Proliferative diabetic retinopathy with vitreous haemorrhage and tractional retinal detachment

Blood investigation and control of systemic factors - Glycemic control, Haemoglobin level, renal function including 24 hour urine protein, lipid levels and control of blood pressure

OCT (Optical Coherence Tomography) - to assess type and severity of macular edema
Ultrasound B scan – Done in cases where there is no fundus view for e.g.: vitreous haemorrhage.

Clinical trials in proliferative diabetic retinopathy in a nutshell

1. Diabetic Retinopathy Study (DRS) 1972-1975
   Patient eligibility criteria was presence of proliferative diabetic retinopathy in at least one eye or severe non proliferative retinopathy in both eyes. One eye of each patient was assigned randomly to immediate photocoagulation (scatter pan retinal treatment, direct local treatment to new vessels and focal treatment for macular edema). The other eye was assigned to follow up without photocoagulation. The eye chosen for treatment was then randomly assigned to either argon laser or xenon arc photocoagulation.

   Conclusion
   • Defined high risk characteristics (HRC) of PDR
   • Scatter PHC decreases the risk of severe vision loss in patients with HRC by 50%
   The study however does not provide clear guidelines for laser treatment in eyes with less severe retinopathy without HRC.

2. Early treatment of Diabetic Retinopathy (ETDRS) 1980-1985
   This study enrolled 3700 patients with bilateral Non proliferative diabetic retinopathy with or without macular edema.

   Conclusion
   • Focal photocoagulation should be considered for eyes with CSME
   • Scatter treatment is not indicated for eyes with mild to moderate non proliferative diabetic retinopathy.
   • As the retinopathy progresses to the severe non proliferative or early proliferative stage, scatter treatment should be considered, especially for patients with Type 2 diabetes and it should be performed without delay for virtually all eyes with high-risk proliferative retinopathy.

3. DRVS (Diabetic Retinopathy Vitrectomy Study)
   Patient eligibility criteria were presence of recent severe vitreous haemorrhage (within 5 months) or very severe proliferative retinopathy with extensive active fibrovascular proliferations and useful vision in patients with Type 1 and Type 2 diabetes mellitus. Early vitrectomy 1-6 months after the onset of haemorrhage. Conventional management includes vitrectomy if haemorrhage fails to clear during a waiting period of 12 months or if retinal detachment involving the centre of the macula develops at any time.

   Conclusion
   • For eyes with recent severe vitreous haemorrhage, early vitrectomy provided a greater chance of prompt recovery of visual acuity although greater, is more pronounced for patients with Type 1 diabetes.

   At the present time, it should be noted that the results of DRVS were obtained before the development of modern vitrectomy instrumentation, techniques and endlaser photocoagulation. With these techniques, the results are more favourable. Nowadays in general, the recommended timing of vitrectomy for severe diabetic vitreous haemorrhage is before 3 months for Type 1 diabetics and 6 months for Type 2 patients.

Treatment Strategies in PDR

1. Laser Photocoagulation
   The classic and established indication of laser treatment in proliferative retinopathy is the presence of neovascularisation with high risk characteristics (HRC).

   The recommended guidelines for treatment of PDR summarised in table 1

   Table 1- Recommendation for PDR treatment

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Treatment recommended</th>
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<tbody>
<tr>
<td>PDR with high risk characteristics (HRC)</td>
<td>Full scatter PRP (Pan retinal Photocoagulation) Avoid areas of tractional RD and fibrous proliferation Mild – moderate burns</td>
</tr>
<tr>
<td>Iris or angle neovascularisation</td>
<td>Early PRP irrespective of presence or absence of retinal HRC.</td>
</tr>
<tr>
<td>Consider systemic factors for decision - i.e. eyes with very severe Non proliferative diabetic retinopathy or eyes with PDR without high risk characteristics.</td>
<td>Role of PRP in such cases is uncertain 12, 13 and individual decisions are to be made</td>
</tr>
<tr>
<td>Severe ischaemia i.e. extensive retinal haemorrhages, capillary non-perfusion, multiple soft exudates (high risk of anterior segment neovascularisation)</td>
<td>consider PRP</td>
</tr>
<tr>
<td>Early PDR and maculopathy</td>
<td>macular treatment preferably done first followed by PRP 2-4 weeks later</td>
</tr>
<tr>
<td>Maculopathy + PDR with HRC</td>
<td>focal macular treatment can be combined with nasal half PRP, followed 2-3 weeks later with completion of PRP</td>
</tr>
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   Special situations for PRP
   Various factors known to worsen the retinopathy may influence the decision to initiate treatment in eyes with severe Non proliferative diabetic retinopathy (NPDR) or PDR.
without HRC. These factors include pregnancy, nephropathy, cardiac failure, carotid artery disorders, cataract surgery and yag laser capsulotomy, uncontrolled blood sugars, recent institution of Insulin in a patient of NIDDM with long-standing uncontrolled blood sugars, poor patient follow-up etc. This is important in our country where various social and economic factors reduce the follow up rate.

Hence the decision to treat or not to treat hence has to take into account all these factors, besides the guidelines provided in the randomized clinical trials.

**Technique of LASER treatment**
The commonest wavelengths used are Double frequency Nd:Yag (532 nm), Argon green and blue-green using the slit-lamp delivery system or indirect ophthalmoscopic delivery. In case of hazy media due to cataract or vitreous haemorrhage, Krypton red or diode red laser (814nm) can be used.

The initial limits of scatter laser are:
- Posterior: Superiorly & inferiorly - temporal vascular arcades
- Nasal - ½ DD from disc
- Temporal - 2 DD from fovea centre
- Anteriorly - Equator (recognized by ampulla of vortex veins)

General rule is to treat the inferior quadrant first (since if by any chance vitreous bleed occurs). A total of 1600-3000 burns are placed in two or more sittings, carefully avoiding the macular area and any areas of tractional elevation of the retina. Typical initial settings on the Nd:Yag Laser would be 500 μ spot size, 0.1 second exposure and 100-150 mw power. The power is gradually increased till a whitish reaction is obtained on the retina.

**Table 2: Grading of retinal burns**

<table>
<thead>
<tr>
<th>Grading of burns</th>
<th>Reaction seen</th>
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</thead>
<tbody>
<tr>
<td>Light</td>
<td>Barely visible retinal blanching</td>
</tr>
<tr>
<td>Mild</td>
<td>Faint white retinal burn</td>
</tr>
<tr>
<td>Moderate</td>
<td>Opaque, dirty white retinal burn</td>
</tr>
<tr>
<td>Heavy</td>
<td>Dense white retinal burn</td>
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</table>

The lesions are placed one burn width apart. Local confluent treatment to small, flat NVE can be done in addition. Laser treatment should not be applied over major retinal veins, pre-retinal haemorrhages, darkly pigmented chorioretinal scars or within one disc diameter of centre of macula, so as to avoid risk of haemorrhage or large scotomas.

**How does Laser photocoagulation (PHC) work?**
Under normal conditions, diffusion of oxygen from choriocapillaries to inner retina is limited because of high oxygen consuming photoreceptor RPE complex. PHC destroys photoreceptor RPE complex. By decreasing the oxygen consumption, more oxygen is available to diffuse in to the inner retina and vitreous. This reduces stimulus for angiogenesis and induces inhibitors of neovascularisation.

**Follow-up treatment after initial PRP**
ETDRS guidelines for follow-up treatment after initial PRP based on six factors
1. Change in new vessels since the last treatment/last visit
2. Appearance of the new vessels (calibre, degree of network formation, extent of accompanying fibrous tissue)
3. Frequency and extent of vitreous haemorrhage
4. Status of vitreous detachment
5. Extent of photoacoagulation scars
6. Extent of tractional retinal detachment and fibrous proliferation.

Assessment of laser treatment is generally done 2-3 months after the completion of scatter laser.

**Factors favouring additional photocoagulation**
1. Lack of regression within 6-8 weeks of the initial treatment.
2. Active new vessels (tight networks, little fibrous tissue, rapid growth in size).
3. Recurring vitreous haemorrhage, whether the source is visible or not.
4. Extensive intraretinal lesions (venous beading, intra retinal microvascular anomalies (IRMA), blot haemorrhages, retinal edema).
5. Skip areas

2. **Intravitreal Anti VEGF in PDR**
Adjuvant agent to PRP for PDR
Substantial regression of new vessels may take weeks after completion of PRP, and in up to one third of cases, new vessels continue to grow despite initial PRP. In these cases, vitreous hemorrhage may induce visual loss and prevent complete laser. Moreover, macular edema may increase after PRP and cause transient or persistent visual loss. Intravitreal anti VEGF seems to be a useful treatment for PDR minimizing
- a) Risk for exudative complications
- b) Progression of retinal neovascularisation
- c) Vitreous haemorrhage
- d) Deterioration of vision caused by macular edema.

**Pre-treatment of diabetic vitrectomy**
Another important use of intravitreal anti VEGF is in the pre-treatment for diabetic vitrectomy. A recent metaanalysis of all randomised studies demonstrating effect of preoperative adjunct intravitreal bevacizumab (IVB) showed that the incidence of intra-operative bleeding and frequency of endodiathermy were statistically significantly less in the IVB pre-treatment group than in the vitrectomy alone group. The IVB pre-treatment group took significantly less surgical
time than the control group. Postoperative results indicated that reabsorption time of blood was significantly shorter, incidence of recurrent vitreous haemorrhage was almost significantly less (p=0.05), and final best-corrected visual acuity was significantly better in the IVB group than in the control group.

3. Vitrectomy

Indications of vitrectomy in PDR
Media opacity
Surgical intervention for non resolving diabetic vitreous haemorrhage.

Vitreo-retinal traction
Cases of tractional retinal detachment involving or threatening macula, macular heterotopia, progressive fibrovascular proliferation without retinal detachment, and secondary rhegmatogenous retinal detachment.

Progressive fibrovascular proliferation
Rapid progression seen in type 1 eyes and is associated with guarded visual prognosis after vitrectomy because of lack of posterior vitreous detachment.

Tractinal Retinal Detachment
Vitrectomy is generally reserved for cases in which the macula is involved or threatened. Chronic macular detachment is associated with poorer anatomic and visual prognoses due to thin, atrophic retina with more extensive and more tightly adherent fibro vascular membranes. Therefore, in cases of TRD involving macula of more than six months, surgery may not be recommended.

Combined Traction and Rhegmatogenous Retinal Detachment Diabetic Maculopathy
Diabetic macular edema
Traction-induced caused by the contraction of a taut, persistently attached posterior hyaloid.

Timing of vitrectomy in PDR

Urgent
Neovascularisation of iris in an eye with a recent vitreous haemorrhage and extensive pre macular haemorrhage
Early surgical intervention
No previous laser treatment
More extensive and vascular fibrovascular proliferation
Fellow eye with rapidly progressive visual loss/ blind
Surgical intervention deferred if Presence of a complete PVD
Extensive prior PRP
Comorbidities contraindicating surgical procedure
Such patients need to be monitored frequently with ultrasonography to rule out retinal detachment.

Surgical Techniques in proliferative diabetic retinopathy
When vitreous haemorrhage is present, a standard pars plana vitrectomy is performed first and the posterior hyaloid face (PHF) is identified; if there is a significant amount of blood behind the PHF, an opening in the PHF is created in order to aspirate the retrohyaloid blood and to gain adequate view of the retina19. It is imperative to release any traction on the retina by existing membranes. Such membranes are almost always vascularized, and thus they cannot be simply peeled from the surface of the retina, as this would result in severe hemorrhage and/or tearing of the retina19, 20. Segmentation, delamination, en-bloc delamination and bimanual dissection represent the main surgical techniques employed in diabetic vitrectomy.

Segmentation-
Segmentation involves the vertical cutting of epiretinal membranes into small segments, and this can be accomplished either with vertically cutting scissors or a mechanized vitreous cutter. Segmentation is used to release circumferential traction when other methods, such as delamination, are made difficult by very mobile retina in the presence of a retinal break. When segmenting membranes, it is not necessary to remove the membranes completely, leaving small, circumscribed remnants centered on the neovascular pegs. The disadvantage of the segmentation technique is that the residual islands of fibrovascular tissue may encourage reproliferation and recurrent bleeding.

Delamination-
The risk of postoperative bleeding may be reduced by a complete removal of fibrovascular tissue from the retina using horizontally cutting scissors to sever the individual neovascular pegs from the retinal surface. The aim is to cut rather than avulse the neovascular pegs, as this would lead to perioperative hemorrhage from the sidewall of a retinal vessel, which may prove to be difficult to control. Finding the correct plane between the posterior hyaloid and the retina near the vascular epicenter is crucial, in order to avoid iatrogenic tears.19, 21

En-bloc delamination-
En-bloc delamination is preferable to segmentation because it enables us to completely remove all the fibrovascular tissue from the retinal surface. In this technique, the posterior hyaloid is kept partially intact in order to use the continuing antero-posterior traction to elevate the epiretinal membranes during dissection. A small window in the partially detached posterior hyaloid is made so that a horizontally cutting scissors can be introduced into the retrohyaloid space.
Gentle traction immobilizes the fibrovascular membrane and the underlying elevated retina exposing areas of adhesion between the membrane and the retina facilitating its excision. The light pipe or illuminated forceps can be used to turn the membrane over and facilitate the dissection. When the membranes have been completely separated from the retina the remaining posterior hyaloid complex can be removed with the vitreous cutter.

Techniques for vitrectomy in PDR require the combination of delamination and segmentation techniques, because of the difficulties in completely separating the fibrovascular membranes from a mobile detached retina.

**Bimanual surgical technique**
This method can be employed in complicated cases using a separate light source, which allows the surgeon to use two instruments for dissection.  

**Advances in diabetic vitrectomy**

**Viscodissection**
Several adjunctive manoeuvres like visco-dissection of membranes involves injecting viscoelastic material in between the sheet of fibrovascular membranes and the retina and can be useful in thin, atrophic retinas. Visco-dissection distributes the forces more broadly and evenly, better defines fibrovascular stumps.

**Vitrectomy with ILM (Internal Limiting Membrane ) peeling**
Vitrectomy with or without ILM peeling is generally an effective procedure in retinopathy reducing diabetic macular edema and improving visual acuity. A prospective, comparative, nonrandomized study evaluating the efficacy of pars plana vitrectomy (PPV) with and without inner limiting membrane (ILM) peeling for persistent diffuse clinically significant macular edema showed structural improvement but with limited visual improvement after ILM peeling.

**Tamponading agents in diabetic vitrectomy**
Intravitreal tamponading agents like silicone oil can be used as adjunctive measures in vitrectomy for proliferative diabetic retinopathy. This enables rapid visual recovery, fundus examination during postoperative follow up, reduces vascular proliferation and post operative bleeding. Silicone oil in addition also helps in long term tamponade of multiple retinal breaks and reduces the chance of proliferative vitrecteropathy. Anterior segment neovascularisation regresses after vitrectomy in eyes with silicone oil, possibly via blocking diffusion of vasculoendothelial growth factor (VEGF).

**Conclusion**
Awareness of diabetic retinopathy and prompt referral of diabetics play a crucial part in the management of this potentially vision threatening condition. Diabetic retinopathy screening camps have a long way to go for the early case detection. Every diabetic patient must be informed by their physicians/ opticians/ ophthalmologists about risk of retinopathy and need for periodic dilated eye retinal examinations. Proper treatment and follow-up of these patients is essential for preservation of vision in many of these patients. In eyes not amenable to laser treatment or where the retinopathy shows progression even after laser treatment, early and appropriate vitreoretinal surgery is successful in regaining some useful vision.

**REFERENCES**

22. Pars Plana Vitrectomy With and Without Peeling of the Inner Limiting Membrane for Diabetic Macular Edema, Retina 2006 Jan 26 (1)5-13

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