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EDITORIAL

Diabetic Retinopathy: An Ophthalmologist Perspective

Sumita Sethi

Introduction

Diabetic Retinopathy (DR), one of the leading causes of blindness worldwide, is a classic example of microvascular damage that occurs in the body because of diabetes. The prevalence of DR varies as per the different population based studies; pooled data analysis reveals a crude prevalence of 40% of DR and 8% of severe retinopathy and macular oedema[1]. It is well accepted that after 20 years of onset of Diabetes, almost all subjects with type-I diabetes and 60% of those with type-II diabetes will have some degree of retinopathy. The Diabetes control and complications trial (DCCT)[2] and the United Kingdom Prospective Diabetes Study (UKPDS)[3] concluded decisively that a stringent control of blood sugar delays progression of DR; though there is an initial phase of worsening of DR but that is followed by stabilization. Besides for duration and control of diabetes, there are certain other factors which affect the onset and progression of DR, these include hypertension, puberty, pregnancy, obesity, hyperlipidemia and certain genetic factors.

Pathogenesis of Diabetic retinopathy

Hyperglycemia, the major etiological factor for DR damages retinal vasculature in multiple ways. Though the exact mechanism is poorly defined, multiple biochemical pathways have been proposed to demonstrate the significant correlation between microvascular complication of DR and hyperglycemia.

Non enzymatic binding of glucose to protein side chains leads to formation of advanced glycation end products (AGE); these have been associated with pericyte loss and microaneurysm formation[4].

Increased polyol metabolism of glucose could lead to altered signalling of pathways involving protein kinase-C (PKC). This could result in various cellular changes leading to endothelial cell damage[5].

Chronic hyperglycemia could produce oxidative stress and damage to retinal vasculature.

Capillary nonperfusion leads to ischemia which further leads to liberation of Vascular Endothelial Growth Factor (VEGF)[6].

Various other growth factors like Growth hormone, Insulin like growth factor-1 (IGF-1), Transforming growth factor-β, Angiopoietin-2, Pigment epithelium derived factor and Connective tissue growth factor (CTGF) could play an active role in development of various structural changes in retinal vasculature.

Clinical features of DR

In DR, damage is caused by both microvascular occlusion and leakage from breakdown of blood-retinal barrier. **Microaneurysms**, the earliest clinically detectable feature on fundoscopy are actually outpouching of the capillaries and appear as tiny red dots**. Retinal haemorrhages** are seen in the posterior pole and can be located both superficially (flame shaped) and in the deep layers (dot-blot haemorrhages). The most important sequel of DR is the occurrence of capillary closure. **Intraretinal microvascular abnormalities (IRMA)** refer to vascular abnormalities occurring adjacent to areas of capillary closure either due to dilated pre-existing capillaries or intraretinal neovascularization. Shimuzu's studies on fluoresce in angiography have established a 4-step scale for severity of neovascularization; 1-none, 2-new vessel on retina alone, 3-new vessel involving disc and 4-new vessel in anterior chamber[7]. **Soft exudates**, seen as opalescent areas, are discrete areas of retinal infarction. **Hard exudates**, seen as discrete intraretinal deposits, occur due to extravasation of lipoproteins and may form a circinate pattern around foci of leaky capillaries.

Broadly diabetic retinopathy is classified into non-proliferative and proliferative varieties; proliferative variety being characterized by occurrence of new vessels at the disc (NVD) or elsewhere in the retina (NVE) (figure-1 a,b). The severe non-proliferative state is referred to as pre-proliferative retinopathy (figure-2). The 4:2:1 rule is usually used to identify the pre-proliferative phase i.e. 4 quadrants with severe haemorrhages and microaneurysm, 2 quadrants with venous beading and 1 with moderate IRMA[8].

Macular Oedema can accompany any stage of DR

It results from increased vascular permeability from retinal capillaries and from IRMA and microaneurysms, thus leading to collection of fluid within the layers of retina. Although oedema anywhere in the posterior pole can be termed as macular oedema, the significance of vision disturbance and need for management will depend on involvement of the centre of fovea. As per the Early Treatment for Diabetic Retinopathy Study (ETDRS), macular oedema is considered present if:

1. Retinal oedema at or within 500 µm (1/3rd of the disc diameter) of the fovea.
2. Hard exudates at or within 500 µm of the fovea if associated with adjacent retinal thickening
3. Retinal oedema one disc diameter (1500 µm or larger), any part of which is within one disc diameter of the fovea[9].

In absence of a timely diagnosis and initiation of treatment, the disease may proceed to an **advanced stage**. Vitreous plays an important role in determining progress of the disease. In case of posterior vitreous detachment (PVD), new blood vessels in the retina are pulled and cause bleeding. New vessels at the disc could also grow directly into vitreous cavity and produce vitreous haemorrhage. Along with haemorrhage, some amount of vitreous condensation takes place causing fibrosis in the vitreous cavity; this leads to progressive fibrovascular proliferation and retinal traction. Focal traction could lead to conical retinal detachment while broad based traction could lead to extensive detachments. Besides for causing changes in retinal and vitreous, neovascularisation could occur in the iris too leading to neovasular glaucoma and blind painful eye.

Management of Diabetic Retinopathy

1. A timely detection of the disease in the early treatable stage could help in initiation of timely treatment and prevent visual loss. The importance of a routine comprehensive eye evaluation can thus not be underestimated.
2. There is definite role of effective glycaemic control, control of hypertension and serum lipid control to reduce both the incidence and progression of the disease. A target level of HbA1C of <7% is recommended in subjects with DR and lowering of its levels is associated with reducing occurrence and progression of DR[9].
3. **Specific investigations: Fundus Fluoresce in Angiography (FFA)** could pick up areas of IRMA and demonstrate extent of capillary closure and state of blood retinal barrier. It enables better treatment strategy planning for macular oedema by identifying the variety of macular oedema and its perfusion status. Macular oedema can be classified by FFA into focal, diffuse and ischaemic variety. **Optical Coherence topography (OCT)** enables evaluation of the macula at fine resolution and elicits several features of macular oedema. Thickening of the central macula serves as a useful guide to evaluate efficacy of various treatment modalities. In cases of opaque media, **Ultrasonography B-scan (USG)** is useful to evaluate status of the retina and accordingly plan the surgical treatment.

Specific treatment modalities

Laser photocoagulation: Transpupillary delivery of blue green light of Argon laser with spot size of 50-500 μ is used to produce deliberate retinal burns. Although the exact mechanism of action is not known, it is accepted that destruction of some areas of the retina permits blood and oxygen to be delivered to the rest of the retina thus improving the overall ischemic status. Scatter laser/Pan-retinal photocoagulation is the commonest modality of delivery of retinal burns. In this, the peripheral retina is ablated sparing only the key hole shaped central area including the disc, macula and maculopapillary nerve fibre. Laser treatment is also the modality of choice for treating diabetic macular oedema; either in form of focal laser for treatment of focal lesions or grid laser for treatment of diffuse areas of leakage.

Anti-VEGF drugs

VEGF has been established as the mediator of most of the proliferative responses in DR. Though the precise role of anti-VEGF drugs in treatment of DR is not yet well defined, intravitreal injections of these drugs have been found to have significant role in treatment of neovascularization associated with the disease. Presently there are 3 anti-VEGF drugs available commercially; Ranibizumaz, Pegaptanib sodium and Bevacizumab[10]. The role of these drugs in macular oedema is well defined and its accepted that they play a significant role in reducing macular oedema and improving vision, though there is significant chance of recurrence despite repeated injections.

Corticosteroids

Due to their potent anti-inflammatory and VEGF downregulatory effect, intravitreal or subtenon's injection of corticosteroids have proved effective in treatment of diabetic maculopathy. However the results are inconsistent, recurrences very common and there are multiple associated side effects like elevated intraocular pressure and steroid induced cataract[11].

Surgical intervention

When medical measures fail to control the disease or when patient presents with advanced disease, surgical approach is required. Non-clearing vitreous haemorrhage, tractional retinal detachment involving the macula and diabetic macular oedema with premacular traction are some of the indications for surgical intervention requiring vitrectomy and removal of blood and fibrovascular tissue. Additional procedures that may be required are fluid air exchange, silicon air injection and endo laser photocoagulation.

Newer concepts in treatment of Diabetic Retinopathy

DR is a major public health problem and a subject for extensive research worldwide. Numerous inventions have been made recently, though not all have entered the clinical field. PASCAL (Pattern scan laser) with much less duration of laser exposure and semiautomated delivery of preset pattern leads to an advanced precision, less burn speed and less collateral damage is being considered superior to the routine Argon laser[12]. Recently role of 2 PKC inhibitors (Ruboxistaurin and PKC412) is being evaluated to study their role in reducing microvascular complications of DR[13]. Somatostatin analogues with their role of inhibiting angiogenesis directly through somatostatin receptors on endothelial cells or indirectly by inhibition of post receptor signalling events have been under evaluation in subjects with early proliferative changes[14]. Short term high dose anti-oxidant therapy with oral vitamin E could help in normalizing retinal hemodynamics and is under evaluation.

While the current treatment concentrates on the proliferative component of the disease, more recent research has shown that pathogenesis of the disease contains both a neurodegenerative and vasodegenerative component. There is great potential for the use of stem cells in conferring both neuro and vasoprotection on the diabetic retina[15].

Figure-1: Fundus photograph of a patient with proliferative diabetic retinopathy showing (a) neovascularisation at disc (NVD) and (b) neovascularisation elsewhere (NVE).

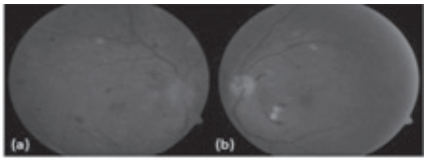
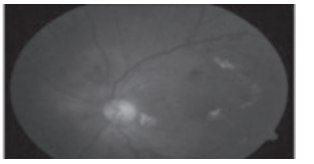


Figure-2: Fundus photograph of a patient with severe non-proliferative diabetic retinopathy showing venous beading in more than 2 quadrants and clinically significant macular oedema (CSME).



Dr. Sumita Sethi

Assistant Professor of Ophthalmology,
BPS Goverment Medical College for women,
Khanpur, Sonepat, Haryana, India.
E-mail id: sumitadrss@rediffmail.com.
Telephone Number: +91 9812533851

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