# REVIEW ARTICLE

# DIABETIC RETINOPATHY – RECENT DEVELOPMENTS AND CHALLENGES

**Sameer Shahid Amin, Muhammad Ahsan Mukhtar**

Military Hospital, Rawalpindi

## INTRODUCTION

Diabetic Retinopathy is the leading cause of new blindness in working population. Over 135 million individuals are afflicted with diabetes across the world. Prevalence of diabetic retinopathy is increasing worldwide due to increasing number and prolonged survival of diabetic patients. The prevalence of diabetes is approximately 2% in U.K population although prevalence among Asian groups can be as high as 16% [1]. Increasing survival of patients with diabetic retinopathy, resulting in higher incidence severe, sight-threatening complications, compounds the problem. The 5 year survival rate for patients with proliferative disease 50 years ago was 30% compared with today's figure of 90% for patients of early onset diabetes and 60% for patients with late onset diabetes[2]. There is evidence that retinopathy begins to develop at least 7 years before the clinical diagnosis of type 2 diabetes [3]. Successful management of diabetic retinopathy via a combination of glucose control, laser therapy, and vitrectomy represents one of the most striking achievements of modern ophthalmology.

Diabetic macular edema is a manifestation of diabetic retinopathy that produces loss of central vision. The prevalence of diabetic macular edema is ~20% in diabetic patients [4]. Currently, the only demonstrated means to reduce the risk of visual loss from diabetic macular edema are intensive glycemic control and laser photocoagulation [5-7]. If fundus examinations are initiated prior to the development of significant retinopathy and repeated periodically, and if the recommendations of the Early Treatment Diabetic Retinopathy Study (ETDRS) are followed with respect to the management of subsequent diabetic macular edema or neovascularization, the risk of severe visual loss is less than 5%. The current review will discuss the pathophysiology, screening, medical treatment, and future research for diabetic Retinopathy.

**Correspondence:** Lt Col Sameer Shahid Ameen, Classified Eye Specialist, MH Rawalpindi.

## PATHOPHYSIOLOGY

Several biochemical pathways have been proposed to link hyperglycemia and microvascular complications. These include polyol accumulation, formation of advanced glycation end products (AGEs), oxidative stress, and activation of protein kinase C (PKC). These biochemical pathways are associated with production and signaling of growth factors such as VEFG, growth hormone, IGF-I, transforming growth factor-ß (TGF-ß), and pigment epithelium–derived growth factor (PEDF). The VEGFs are a family of proteins that are mitogenic for vascular endothelial cells and increase vascular permeability. However, increased expression of VEGF has been demonstrated in diabetic retinopathy [8]. Growth hormone and IGF-I have been suspected of playing a role in the progression of diabetic retinopathy. Diabetic retinopathy also exhibits features of both microvascular occlusion and leakage. Capillary changes include loss of pericytes, thickening of the basement membrane and damage and proliferation of endothelial cells. Microvascular leakage occurs because of leakage of plasma constituents into the retina and lead to diffuse or localized retinal edema.

### Early Non Proliferative Diabetic Retinopathy

Microaneurysms are the first ophthalmoscopically detectable change in

diabetic retinopathy seen as small red dots in the middle retinal layers. When the wall of a capillary or microaneurysm is weakened enough, it may rupture, giving rise to an intraretinal hemorrhage. If it is deep in the inner nuclear layer or outer plexiform layer, it usually is round or oval ("dot or blot"). If the hemorrhage is superficial in the nerve fiber layer, it takes a flame or splinter shape indistinguishable from a hemorrhage seen in hypertensive retinopathy. Macular edema and retinal thickening is an important manifestation of NPDR and represents the leading cause of legal blindness in diabetics. The intercellular fluid comes from leaking microaneurysms or from diffuse capillary incompetence. The pockets of fluid in the outer plexiform layer, if large enough, can be seen as cystoid macular edema. If the leakage of fluid is severe enough, lipid (hard exudates) may accumulate in the retina; again, the outer plexiform layer is first to be affected.

### Advanced Non Proliferative Diabetic Retinopathy

In advanced NPDR, signs of increasing inner retinal hypoxia appear, including multiple retinal hemorrhages, cotton-wool spots, venous beading and loops, intraretinal microvascular abnormalities (IRMA), and large areas of capillary nonperfusion depicted on fluorescein angiography. Cotton-wool spots, also called soft exudates or nerve fiber infarcts, result from ischemia, not exudation. Local ischemia cause effective obstruction of axoplasmic flow in the normally transparent nerve fiber layer, the subsequent swelling of the nerve fibers gives cotton-wool spots their characteristic white fluffy appearance.

### Proliferative Diabetic Retinopathy

Approximately 50% of patients with severe NPDR progress to proliferative retinopathy within 1 year [9]. Proliferative vessels usually arise from retinal veins and often begin as a collection of multiple fine vessels. When they arise on or within one disc diameter of the optic nerve head they are referred to as NVD (neovascularization of the disc). When they arise farther than one disc diameter away, they are called NVE (neovascularization elsewhere). Unlike normal retinal vessels, NVD and NVE both leak fluorescein into the vitreous. As PDR progresses, the fibrous component becomes more prominent, with the fibrotic tissue being either vascular or avascular. The fibrovascular variety usually 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. Vitreous traction is transmitted to the retina along these proliferations and may lead to tractional retinal detachment.

## DIAGNOSIS

Direct ophthalmoscopy is the most commonly used technique to monitor for diabetic retinopathy. However, undilated ophthalmoscopy, especially by non–eye care providers has poor sensitivity compared with stereoscopic seven-field color photography [10]. Under typical clinical conditions, direct ophthalmoscopy by non-ophthalmologists has a sensitivity of ~50% for the detection of proliferative retinopathy [11]. Other techniques used in the detection of diabetic retinopathy, include indirect ophthalmoscopy, fluorescein angiography, stereoscopic digital and color film–based fundus photography, and mydriatic or nonmydriatic digital color or monochromatic single-field photography [12].

The latest mean of diagnosis and monitoring progression of diabetic macular edema is Optical coherence tomography which provides images by projecting a pair of near-infrared light beams into the eye. The resulting interference pattern from these beams is dependent of the thickness and reflectivity of the retinal structures and is detected by the measuring system [13]. The images produced appear to be cross-sections

of the retina and allow the thickness of the retina to be measured. The thickness of the retina may allow diabetic macular edema to be followed in a quantitative manner [14].

# TREATMENT

Several studies have proven that the current treatment of diabetic retinopathy is of high quality.

## Glycemic Control

Diabetic Control and Complication Trial (DCCT) showed that tightened control of diabetes could reduce the risk of late complications. Patients were followed up for an average of 7 years. There was a favorable reduction in progression and severity of diabetic retinopathy in intensive treatment group (27% vs. 76%) [15]. Glycemic control is protective for all levels of control; there is no glycemic threshold below which a reduction in microvascular complications is not observed. Currently, the recommendation is for maintenance of glucose levels as near normal as possible [16].

## Management of Co-Existing Medical Problems

Blood pressure control, management of impaired renal function, serum lipid control and anti platelet therapy are important to prevent rapid progression of diabetic retinopathy.

## What is the End Point of Pan Retinal Photocoagulation (PRP)

The purpose of Diabetic Retinopathy study (DRS) was to discover whether laser photocoagulation could reduce blindness from proliferative diabetic retinopathy [17,18]. DRS showed that the application of 1500 burns with scatter treatment was effective in halving the rate of severe visual loss. The goal of PRP is to arrest or to cause regression of the neovascularization. The recommended therapy is 1200-2000 laser burns delivered through the Goldmann lens. Burns should be intense enough to whiten the overlying retina, which usually requires a power of 200-600mW and duration of 0.1 second. Such treatment makes sense, not only from the humanitarian point of view, but also from a cost-effectiveness view.

The Early Treatment Diabetic Retinopathy Study found that PRP significantly retards the development of High risk characteristics (HRC) in eyes with very severe NPDR and macular edema.[19] Eyes with HRC are defined as those with NVD greater than one fourth to one third the disc area, those with any NVD and vitreous hemorrhage, or those with NVE greater than one half the disc area and vitreous or preretinal hemorrhage. Nevertheless, the Early Treatment Diabetic Retinopathy Study concluded that scatter photocoagulation was not helpful in eyes with non-proliferative retinopathy except in eyes having high risk characteristics.

PRP often causes decreased visual acuity by increasing macular edema or by causing macular pucker." Fortunately, the edema frequently regresses spontaneously over 6 months, but the visual field usually is moderately, but permanently, decreased. Color vision and dark adaptation, which often are already impaired, also are worsened by PRP [20].

When deciding whether further PRP is required or not, the importance of vitreous is paramount. If a complete posterior vitreous detachment (PVD) is present, there is no scaffold for new vessels to grow into vitreous. In this instance, persistence of new vessels may be tolerated. Fully attached vitreous may lead to recurrent vitreous hemorrhage due to active new vessels and tractional retinal detachment necessitating prompt application of PRP.

# MACULAR EDEMA

Macular edema affects approximately 20% of diabetic patients with disease duration of 20 years or more and is the main reason for reduced vision in this population [21].

Clinically significant macular edema (CSME) with in one disc diameter of fovea is present in 9% of diabetics [22]. It is also more common in patients with more severe diabetic retinopathy and can limit improvement in eyes with successfully managed proliferative disease [23]. There is clear benefit of focal laser photocoagulation for reducing visual loss in such patients.

## HOW SHOULD WE TREAT DIABETIC MACULAR EDEMA

### Surgical Treatment – What is the Best Timing

Vitrectomy surgery has been demonstrated to be effective for the treatment of non-clearing vitreous hemorrhage, tractional detachments, and active progressive PDR. The results of vitrectomy and endolaser for diabetic vitreous hemorrhage in absence or retinal detachment are good and this treatment should be considered at much earlier stage.[24] Surgery should be advised if there is no clearing of vitreous hemorrhage at 3 months after onset. There are now reports in the literature suggesting that vitrectomy surgery may be helpful in eyes with refractory macular edema [25]. In one study, vitrectomy with peeling of posterior hyaloid was done and 80% patients experienced significant visual improvement [26] but another randomized trial of vitrectomy for macular edema in the absence of visible traction showed no benefit in treatment group compared with controls treated with further grid laser [27]. Therefore, the role of vitrectomy in diabetic macular edema currently remains unclear. The efficacy of vitrectomy surgery will require investigation with a randomized clinical trial.

### Intravitreal Corticosteroids

The frequency of an unsatisfactory outcome following laser photocoagulation in some eyes with diabetic macular edema is around 50% and has prompted interest in other treatments. Recently, delivery of corticosteroids via the vitreous cavity to treat diabetic macular edema has generated significant interest. The rationale for the use of corticosteroids to treat diabetic macular edema follows from the observation that the increase in retinal capillary permeability that results in diabetic macular edema may be caused by a breakdown of the blood retina barrier mediated in part by VEGF [28]. Triamcinolone acetonide is the corticosteroid currently used by ophthalmologists in the clinical setting because it is a readily available pharmacologic agent. Currently, the typical dose of triamcinolone acetonide used to treat eyes with diabetic macular edema is 4 mg in a volume of 0.1 ml [29]. It was first proposed, in 1999, as a treatment for diabetic macular edema because of the safety profile demonstrated in animal models, prior clinical experience with other retinal diseases, and the rationale of attenuating the VEGF-mediated retinal capillary permeability that is presumed to contribute to diabetic macular edema. The use of intravitreal triamcinolone acetonide is now widespread among ophthalmologists who specialize in the treatment of retinal disease [30]. However, the enthusiasm for the use of intravitreal steroids is often tempered by the adverse effect profile seen in these published series and in anecdotal reports. These adverse events are related to both the injection itself and the potential toxicity of corticosteroids. Injection-related events include bacterial infection of the eye (endophthalmitis), vitreous hemorrhage, and retinal detachment. The potential toxicity of corticosteroids includes the development of cataracts and glaucoma. After intravitreal injections of 25 mg of triamcinolone acetonide, an IOP elevation can develop in about 50% of eyes, starting about 1–2 months after the injection. In the vast majority, IOP can be normalized by topical medication, and returns to normal values without further medication about 6 months after the injection [31,32]. Another unresolved issue with the use of this technique is that commercially available Kenacort is formulated specifically for intrabursal and

intramuscular use and not for intravitreal use, necessitating "off-label" use of Kenacort by the ophthalmology community. There have been several anecdotal reports of inflammatory reactions, possibly to one of the excipients in the Kenacort formulation, following intravitreal injection of Kenacort. These sterile inflammatory reactions (called Non-infectious endophthalmitis) are often difficult to distinguish from a post injection bacterial infection of the eye [33].

## PHARMACOLOGICAL INHIBITORS OF VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

The development of new blood vessels from pre-existing ones is called angiogensis. Angiogenesis plays an important role in pathological process in diabetic retinopathy. This has led to isolation of angiogenic stimulators collectively known as VEGF. Several agents targeting angiogenesis have been developed.

### Macugen

Pegaptanib (Macugen) is a 28-base oligonucleotide (aptamer) that binds VEGF [34]. Preliminary analyses suggest that this agent is effective against the neovascular form of age-related macular degeneration. Macugen is currently in being investigated in a phase 3 clinical trials on Diabetic macular edema (DME).

### Lucentis

Lucentis (ranibizumab) is an antibody fragment directed against VEGF. There are plans to investigate this product in the treatment of DME [35].

## CONCLUSION

Diabetic retinopathy is still a leading cause of blindness. However, our understanding of the pathophysiology of the disease is increasing as new biochemical pathways are identified. Our ability to diagnosis and classify retinopathy is also improving. In addition, the treatment of diabetic retinopathy involves not just laser photocoagulation and vitrectomy surgery but now also includes control of blood glucose, hypertension, and serum lipids. Intravitreal injection of triamcinolone effectively reduces macular thickening due to diffuse diabetic macular edema, at least in the short term. Further studies are required to demonstrate that it provides visual benefit. In the near future, clinical trials of several pharmacologic agents may lead to the introduction of additional treatments and reduction in the frequency of visual loss.

Despite improvements in treatment of diabetic retinopathy, the management of progressive changes remains a challenge and many problems have still to be surmounted.

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