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DIABETIC RETINOPATHY UPDATE

# Diabetic retinopathy – An update

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Laser

**Abstract** Management of diabetes should involve both systemic and ocular aspects. Control of hyperglycemia, hypertension and dyslipidemia are of major role in the management of diabetic retinopathy. In the ocular part; laser treatment remains the cornerstone of treatment of diabetic macular edema (focal/grid), severe non-proliferative and proliferative diabetic retinopathy (panretinal photocoagulation). There is a strong support to combination therapy. Using one or two intravitreal injections such as anti-VEGF and or steroid to reduce central macular thickness followed by focal or grid laser to give a sustained response may offer an alternative to treatment in diabetic macular edema. Anti-VEGF were found to be effective as an adjunct therapy in proliferative diabetic retinopathy patient who is going to have vitrectomy for vitreous hemorrhage with neovascularization, panretinal photocoagulation, and other ocular surgery such as cases with neovascular glaucoma and cataract with refractory macular edema.



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## 1. Introduction

Diabetes mellitus is a chronic disorder characterized by the impaired metabolism of glucose due to insulin deficiency or its resistance, leading to hyperglycemia and late development of vascular and neuropathic complications. It is of two types: type 1, primarily caused by autoimmune pancreatic β-cell destruction and characterized by absolute insulin deficiency, and type 2 characterized by insulin resistance and relative insulin deficiency.

In general in the USA; it was estimated that nearly 21 million Americans (or nearly 7% of the US population) fulfilled the diagnostic criteria for diabetes mellitus. Diabetic retinopathy at the time of the diagnosis of diabetes is lower with type I being 0.4% in type I while 7.6% in type II (Roy et al., 2004).

In Saudi Arabia the prevalence of diabetes mellitus was 34.1% in males and 27.6% in females and it increases with age (Alqurashi et al., 2011). In the eastern part of Saudi Arabia the prevalence of diabetes mellitus was 17.2% (Al-Baghli et al., 2010). It is the commonest cause of legal blindness in individuals between the age of 20 and 65 years of age. Recently an extensive work had been done in different aspects of diabetic retinopathy worth reviewing.

## 2. Pathogenesis

Retina is a thin transparent structure constituting of several layers. The cells within the retina fall into one of three groups: (1) neuronal component (photoreceptors, interneurons, and ganglion cells and their interconnections) which give the retina its visual function by converting light to electrical signals. (2) Glial components (Muller cells) are the supporting column in the retina. (3) Vascular components consist of the branches of central retinal artery which, supplies the inner retina while the outer retinal is being supplied by diffusion from choroidal circulation. The retinal vessels maintain blood–retinal barriers due to the single layer of the non-fenestrated endothelial cells with tight junctions between them. The wall of the retinal capillaries is made of endothelial cells, Pericytes (with contractile characteristics) embedded within the endothelium basement membrane. Diabetes will produce its effect on both neuronal and vascular components of the retina. Loss of pericytes, with compensatory synthesis and deposition of extracellular proteins, characterizes early diabetic retinopathy.

Several factors were found to influence diabetic retinopathy including long duration of the disease, age, level of hyperglycemia control, level of blood pressure control, puberty, Pregnancy, hyperlipidemia, hyperviscosity, renal failure and anemia. Hyperviscosity of the blood due to any cause such as dehydration (Alghadyan, 1993) and polycythemia may influence the diabetic retinopathy. More important is the contribution of the biochemical changes associated with hyperglycemia. Knowing these factors will help in a better management; for example in cases of fluid retention cases it will be better first control the underlying causes such as high blood pressure and other systemic causes and the ocular treatment. The need for oxygen differs in different parts of the retina. The thin peripheral retina needs less oxygen and it receives much of its oxygen from the choroid, which may offer relative protection against apoptosis in the face of retinal capillary insufficiency. Perhaps a similar mechanism underlies the apparent protective effect of high myopia and advanced glaucoma on the progression of diabetic retinopathy (Henkind, 1978; McLeod, 2007; Sultanov and Gadzhiev, 1990; Dogru et al., 1998; Klein et al., 1988, 1997).

The exact mechanism by which hyperglycemia causes vascular disruption seen in retinopathy is not clear. Probably the intraocular formation of reactive oxygen species fuels the subsequent pathological, biochemical changes seen in diabetic retinopathy (Fig. 1). These biochemical changes include: (1) protein kinase C is a subclass of the transferases that catalyze the transfer of a high-energy group from a donor (usually ATP) to an acceptor (e.g., protein). It is known that hyperglycemia increases the activity of various Protein kinase C isoforms which were found to play an important role in the

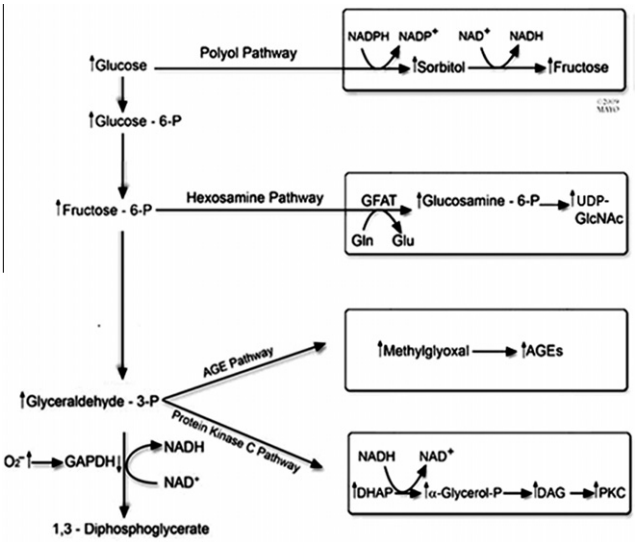


**Figure 1** This schematic shows the four biochemical pathways that lead to diabetic retinopathy. DHAP, dihydroxyacetone phosphate; DAG, diacylglycerol; PKC, protein kinase C; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; AGEs, advanced glycation end products, UDP-GlcNAC, N-acetylglucosamine.

pathogenesis of diabetic retinopathy (Fig. 1). Activation of protein kinase C causes cellular changes (Xia et al., 1996; Miller et al., 1997), leading to: (a) enhanced permeability of retinal vasculature and alterations in retinal blood flow, (b) basement membrane thickening causing ischemia and cellular signaling by vascular endothelial growth factors (VEGFs) leading to ocular neovascularization. (2) The non enzymatic binding of glucose to key protein side chains as a result of hyperglycemia causes glycation of these proteins as seen in hemoglobin $A_1C$ (Brownlee et al., 1984). Animal studies have demonstrated that accumulation of advanced glycation end products (AGE) is associated with microaneurysm formation and pericyte loss whereas animals treated with AGE formation inhibitor (such as aminoguanidine) showed reduced retinal damage (Wautier and Guillausseau, 2001; Hammes et al., 1991). (3) polyol (such as sorbitol) accumulation: Aldose reductase is the first enzyme in the polyol pathway, has a low affinity for glucose at normal concentrations. Hyperglycemia results in increased conversion of glucose into sorbitol. The increase in intracellular sorbitol concentration has been hypothesized to cause osmotic damage to vasculature of the retina (Gabbay, 1975). In animal experiments; polyol was found to be associated with changes similar to those seen in diabetic retinopathy in humans (Frank et al., 1983; Engerman and Kern, 1984). (4) Oxidative stress caused by formation of free radicals as a result of hyperglycemia and the above mentioned biochemical pathways lead to damage to retinal vasculature. It was found that antioxidants such as vitamin E may prevent some of the vascular dysfunction associated with diabetes (Kunisaki et al., 1995; Bursell and King, 1999; Bursell et al., 1999). (5) Growth factors are diverse group of peptides that affect various cellular processes, including metabolic regulation; tissue differentiation; cell growth and proliferation; maintenance of viability and changes in cell morphology (Bursell and King, 1999; Bursell et al., 1999; Aiello et al., 1994; Pouvlaki et al., 2004). The growth factors are synthesized in a variety of cells and have a spectrum of target cells. The presence of various growth factors in retina, vitreous, aqueous humor, and corneal tissues had been demonstrated. These factors include: epidermal growth factor, fibroblast growth factors, transforming growth factors, vascular endothelial growth factor, and insulin-like growth factors. Vascular endothelial growth factor (VEGF), also known as vasculotropin, deserves special attention due to its role in diabetic retinopathy. It is a heparin-binding polypeptide mitogen and has four isoforms. It is one of many cytokines that plays a prominent role in diabetic retinopathy and it is induced by ischemic neurosensory retina. It is a marker of oxidative stress and induces hyperpermeability of macular capillaries contributing to macular edema. It also induces endothelial proliferation and migration consistent with clinical findings of microaneurysm and neovascular membrane formation. It prevents apoptosis of capillary endothelial cells.

### 3. Presentation of diabetic retinopathy

Evaluating the patients will include: (1) complete history and clinical ocular examination including fundus biomicroscopy; (2) stereoscopic color fundus photography; (3) fluorescein angiography will help to determine the origin of the leakage and identify the ischemic areas; (4) optical coherence tomography (OCT) is helpful in determining the response of macular edema to therapy. The morphology of OCT may alter the prognosis (presence of cystic changes are indicative of chronicity and poorer response to therapy) or alter therapy (presence of vitreomacular traction needing surgery). The retina is particularly vulnerable to microvascular damage in diabetes. Retinal damage is caused by both microvascular leakage from breakdown of the inner blood–retinal barrier and microvascular occlusion. Diabetic retinopathy can be classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

**Non-proliferative diabetic retinopathy** characterized by microaneurysm, exudate, hemorrhages and microinfarcts. This further can be classified into mild, moderate and severe depending on the extent of these changes (Table 1). Microaneurysms are outpouchings of capillaries and are among the first clinically detectable signs of retinopathy. They arise due to ballooning of weakened capillary walls or endothelial buds attempting to revascularize ischemic retina. They appear as tiny red dots, commonly temporal to the macula. Although microaneurysms are not fixed features and may even disappear. Sudden appearance of numerous microaneurysms is an indication of worsening retinal ischemia. Hard exudates consist of lipoproteins and other proteins leaking through abnormal retinal vessels. They appear as yellow lipid deposits with a waxy or shiny appearance and may form a circinate pattern around foci of leaking capillaries and microaneurysms. Hemorrhages occur due to rupture of weakened capillaries. They can be small dots or larger blot hemorrhages present within the densely packed deeper layers of retina. The flame shaped hemorrhages occur in the superficial nerve fiber layer. Microinfarcts in the nerve fiber layer (also known as soft exudates or cotton wool spots) appear in advanced stages of NPDR due to vascular occlusion and they appear as white lesions with vague margins when they heal they might form a depressed area due to tissue loss.

The macula is a highly vascularized and its involvement causes a serious impact on visual function. The macula is usually involved with macular edema associated with broken retinal blood barrier or ischemic or both a new vascularization. Macular edema results from leakage from the broken blood–retinal barriers. Movement of fluids both into and out of the body's capillaries, including those of the retina, is dependent upon (1) hydrostatic pressure which is determined by blood pressure and intra-ocular pressure and (2) oncotic pressure which depends on protein content in the capillaries and in the intertrial fluid. The net force pushing fluid out of capillaries is the difference between hydrostatic pressures and oncotic pressures, any disturbance to this equilibrium will result in retinal edema. When the edema involves the macula and affects vision it is called a clinically significant macular edema which is defined as any one of the following: (1) retinal edema within 500 μm (one third of a disk diameter) of the fovea, (2) hard exudates within 500 μm of the fovea if associated with adjacent retinal thickening, (3) retinal edema that is one disk diameter (1500 μm) or larger, any part of which is within one disk diameter of the fovea (Diabetic Retinopathy Study Research Group, 1976) (Fig. 2).

Ischemic maculopathy arises due to extensive microvascular occlusion and may cause severe loss of central vision. Macular ischemia is caused by complex interactions of the cellular and noncellular constituents of the vascular wall. It can be detected early in diabetic retinopathy and becomes increasingly apparent with advancing stages of severity of diabetic retinop-

**Table 1** The early treatment diabetic retinopathy study (ETDRS) grading system (Early Treatment Diabetic Retinopathy Study Research Group, 1991c,e).

| | | |
|---|---|---|
| Non-proliferative diabetic retinopathy (NPDR) | Mild to moderate NPDR | Microaneurysms, intra-retinal hemorrhages, hard exudate ± macular edema |
| | Moderate to severe NPDR | Extensive intra-retinal hemorrhages and/or microaneurysms and/or cotton wool spots, venous beading or intra-retinal microvascular abnormalities (IRMA) |
| | Severe NPDR to very severe NPDR | Plus Cotton wool spots, venous beading, and IRMA, all present in at least two quadrants. This can be simplified by the rule of 4:2:1. Intra-retinal hemorrhages in four quadrants, Venous beading in two quadrants, Severe IRMA in one quadrant |
| Proliferative retinopathy (PDR) | Neovascularization of the disk and /or Neovascularization elsewhere in the retina | |
| | Early PDR | Pre-retinal hemorrhage |
| | PDR with high-risk criteria | High risk = the presence of any of the following:<br>• Vitreous hemorrhage<br>• New vessels on the disk >1/3 DD (most important prognostic factor for the risk of severe visual loss in DR)<br>• New vessels elsewhere >1/2 DD |
| | PDR with advanced eye disease | Tractional retinal detachment, Neovascularization of the iris/angle |

DD = disk diameter, DR = diabetic retinopathy, PDR = proliferative diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, IRMA = intra-retinal microvascular abnormalities.

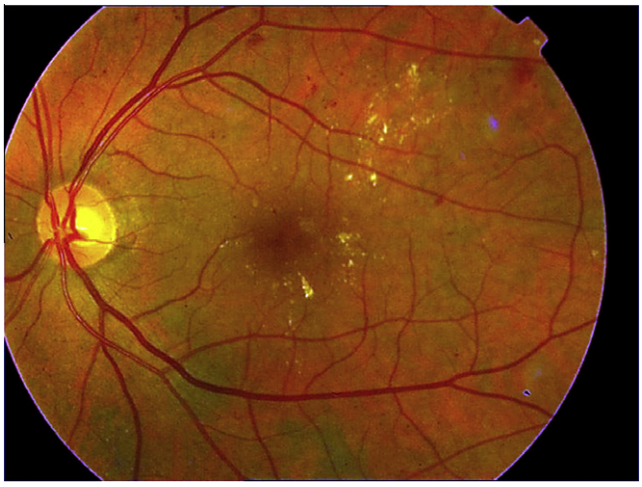

**Figure 2** Moderate non-PDR with CSME.

athy (Patz and Smith, 1991). In patients with decreased vision; it is suspected clinically by funduscopy as areas of "featureless" retina surrounded by typical diabetic microangiopathy. Fluorescein angiography demonstrates the non-filling of macular capillaries, enlargement and irregularity of the foveal avascular zone (FAZ) (a reliable follow up sign), and increased perifoveal intercapillary area (Fig. 3a and b). Optical coherence tomography reveals neurosensory macular thinning.

The optic nerve might be involved in diabetes mellitus (Fig. 4). The vascular supply of the anterior optic nerve is primarily derived from the short posterior ciliary arteries. Due to the effect of diabetes on the blood vessels; diabetes is a risk factor for non arteritic ischemic optic neuropathy (NAION) with high possibility of involvement of the other eye. Other factors may aggravate the diabetic effect. Blood pressure and intraocular pressure influence anterior optic nerve perfusion pressure. Diurnal variations in blood pressure and medications may influence optic nerve perfusion; conditions that can be managed.

**Proliferative diabetic retinopathy (PDR)** is the advanced stage of diabetic retinopathy. It is characterized by new vessel formation commonly arising on the optic disk (New vessels on the disk NVD) or arise on other parts of the retina (new vessel elsewhere or NVE) induced by ischemic changes in the retina and an imbalance between angiogenic and antiangiogenic factors (Fig. 5a and b). The NVD carries the worst prognosis due to many factors including attachment of the vitreous to the optic disk. Early stage of PDR starts as neovascularization and pre-retinal hemorrhages (Table 1). This might progress to vitreous hemorrhages and in late stages it may cause tractional retinal detachment and neovascular glaucoma.

## 4. Management of diabetic retinopathy

Ophthalmologists should not forget the systemic aspect of the disease because management should be directed toward both systemic and ocular aspects of the disease (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2000; Anon., 1995; Writing Team for the Diabetes Control and Complica-

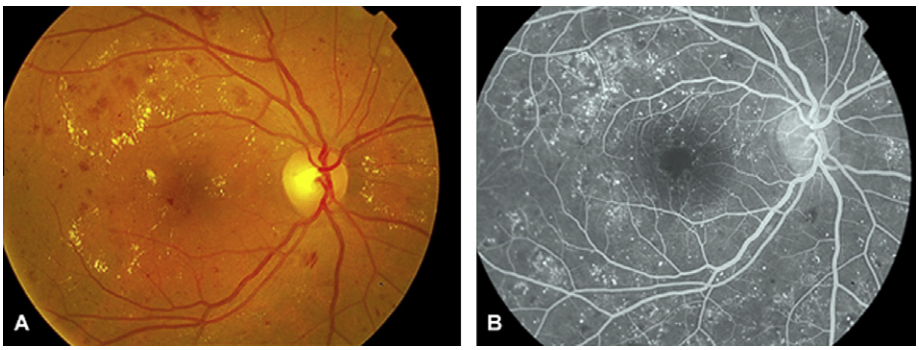


**Figure 3** Non PDR with early sign of ischemia of the fovea; (a) clinical photo and (b) fluorescein angiogram.

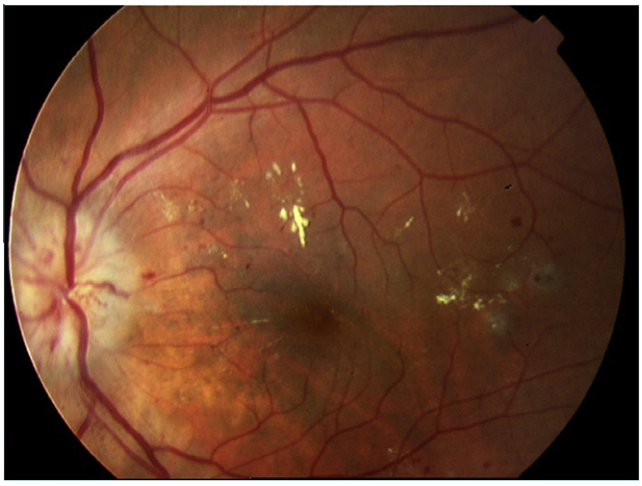

**Figure 4** Ischemic optic neuropathy (note white swelling of the disk).

tions Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2002; Diabetes Control and Complications Trial Research Group, 1993, 1998; UK Prospective Diabetes Study Group, 1998a,b; Egger et al., 1997; American Diabetes Association, 2004; Diabetic Retinopathy Study Research Group, 1981, 1985; Early Treatment Diabetic Retinopathy Study Research Group, 1987, 1991a,b,c,d,e; Rand et al., 1985; Kaufman et al., 1987, 1989; Ferris et al., 1987; Aiello et al., 2010; Ferris, 1996; Davis et al., 1998; Braun et al., 1995; Fong et al., 1999; Diabetic Retinopathy Vitrectomy Study Research Group, 1985, 1988a,b; DRVS, 1985; Flynn et al., 1992; Chew et al., 1995). Systemic management should include controlling blood sugar, blood pressure and serum lipids. (a) In glycemic control; there is a direct and consistent relationship between HbA1c (glycated hemoglobin) level and the incidence of diabetic retinopathy. Effective glycemic control has been demonstrated to reduce both the incidence and progression of diabetic retinopathy. It will be nice to have the target of glycemic control HbA1C to be 6% (Table 2). (b) Hypertension is another important risk factor for the development and/or worsening of diabetic retinopathy. High blood pressure causes endothelial stress with release of VEGF altering retinal autoregulation leading to increased perfusion pressure and injury (Suzuma et al., 2001; Matthews et al., 2004; Estacio et al., 2000; Schrier et al., 2002). Fortunately this risk factor can be treated. It will be nice to have the target of high blood pressure treatment equal to or less than 130/80 mmHg. (c) Renin-angiotensin system is involved in blood pressure control and retinal dysfunction and angiogenesis. It had been shown that angiotensin converting enzyme (ACE) is locally produced by endothelial cells of retinal blood vessels and retinal pigment epithelial cells (Danser et al., 1994; Wagner et al., 1996) and found to be in high concentration in aqueous humor in patients with proliferative diabetic retinopathy (Aydin et al., 2010). The use of ACE inhibitors such as lisinopril and candesartan were found to have favorable effect on the progression of diabetic retinopathy (Chaturvedi et al., 1998, 2008; Sjolie et al., 2008), which might be a good choice for diabetic patients with hypertension. (d) There is a positive correlation between dyslipidemia and progression of diabetic retinopathy or macu-

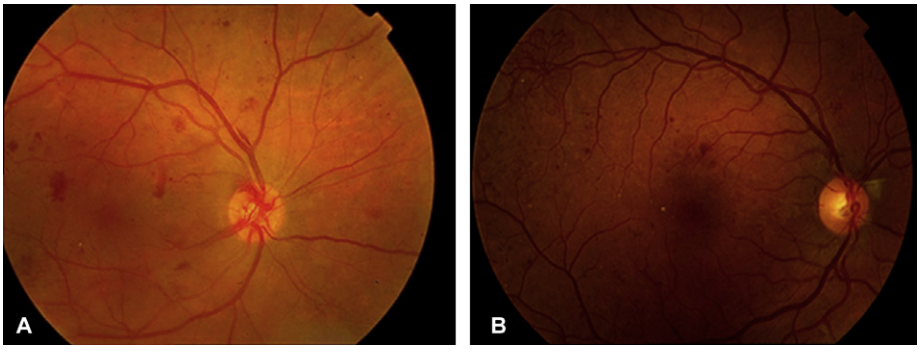


**Figure 5** PDR with NVD in photo (a), and NVE supra temporal in photo (b).

**Table 2** Summary of the important results of some of the studies done on diabetic retinopathy.

| Study | Recommendations |
|---|---|
| DRS | (1) Prompt PRP for eyes with high risk characteristics.<br>(2) NVD is the strongest predictor for severe visual loss and the second strongest predictor was the extent of retinal hemorrhage/microaneurysm<br>(3) Photocoagulation reduces the risk for ocular hypertension apparently by preventing neovascular glaucoma<br>(4) Focal laser treatment for macular edema before PRP and divide PRP in multiple sessions and decrease the intensity of the burn<br>(5) Risk factors for SVL despite PRP during 5 years after randomization: (a) increasing NVD (most important factor), (b) increasing retinal hemorrhages/microaneurysms, (c) increasing retinal elevation (detachment), (d) increasing proteinuria, (e) increasing hyperglycemia, (f) decreasing treatment density |
| ETDRS | (1) Focal/grid laser photocoagulation reduced the risk of moderate vision loss (that is, a doubling of the visual angle) from clinically significant macular edema<br>(2) In patients with type 2 diabetes, it is especially important to consider scatter photocoagulation at the time of the development of severe non-proliferative or early proliferative retinopathy<br>(3) Technique for photocoagulation for PDR: Full PRP include 1200 or more of 500μ burns separated from each other by one half burn width at 0.1 s duration. Confluent treatment of flat NVE<br>(4) Fundus photographic risk factors for progression of diabetic retinopathy: a. Severity of intra-retinal microvascular abnormalities, b. Severity of retinal hemorrhages/microaneurysms, c. Severity of venous beading, d. NOT soft exudates (cotton wool spots)<br>(5) Fluorescein angiographic (FA) risk factors for progression of diabetic retinopathy: a. Fluorescein leakage (particularly the diffuse type), b. Capillary loss and dilation, c. Arteriolar abnormalities (e.g., focal narrowing, pruning, staining), d. FA risk factors offer increased power to predict progression of DR, but do not offer clinically important information over clinical exam and color photography<br>(6) Pars plana vitrectomy in the ETDRS for diabetics with vitreous hemorrhage and retinal detachment<br>(7) Risk factors for high risk PDR and severe visual loss (SVL): (a) higher glycosylated hemoglobin, (b) history of diabetic neuropathy, (c) lower hematocrit, (d) elevated triglycerides, (e) lower serum albumen, (f) type 1 diabetes<br>(8) Transient decrease in accommodative amplitude of 1/3 diopter measured at the 4 month exam following scatter photocoagulation ($P < 0.001$)<br>(9) Causes of severe visual loss (in decreasing order of frequency): (a) vitreous/pre-retinal hemorrhage (despite vitrectomy), (b) macular edema, (c) macular pigmentary change, (d) retinal detachment, (e) narrow or opaque arteries (i.e., ischemia), (f) risk factors for persistent severe visual loss: elevated glycosylated hemoglobin and elevated cholesterol |
| DRVS | (1) Early Vitrectomy for acute, severe vitreous hemorrhage (VH) in diabetic retinopathy especially significant for patients with type 1 diabetes mellitus showed clear cut advantage<br>(2) Early vitrectomy for severe PDR with useful vision. The advantages of early vitrectomy increased with increasing severity of NV<br>(3) Early vitrectomy for severe vitreous hemorrhage in DR. Four years results indicates that eyes with severe VH in patients with type 1 diabetes mellitus benefit from early vitrectomy |
| DCCT 1993 | Long time result in tight hyperglycemic control showed significantly reduced the progression of diabetic retinopathy |
| UKPDS 1998 | Tight glycemic control showed 34% reduction in progression of DR and 47% in reducing the risk of deterioration of vision |

DRS = diabetic retinopathy study, ETDRS = early treatment diabetic retinopathy study, DRVS = diabetic retinopathy vitrectomy study, DCCT = diabetes control complication trials, UKPDS = United Kingdom prospective diabetes study (Aiello et al., 1994, 2010; Pouvlaki et al., 2004; Diabetic Retinopathy Study Research Group, 1976, 1985; Patz and Smith, 1991; Diabetes Control and Complications Trial Research Group, 1993, 1995, 1998; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2000; Anon., 1995; Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, 2002; UK Prospective Diabetes Study Group, 1998a,b; Egger et al., 1997; American Diabetes Association, 2004; Rand et al., 1985; Kaufman et al., 1987, 1989; Ferris et al., 1987; Ferris, 1996; Early Treatment Diabetic Retinopathy Study Research Group, 1991a,b,c,d,e; Davis et al., 1998; Braun et al., 1995; Fong et al., 1999; Diabetic Retinopathy Vitrectomy Study Research Group, 1985, 1988a,b; DRVS, 1985; Flynn et al., 1992; Chew et al., 1995; Suzuma et al., 2001; Flynn et al., 1992; Chew et al., 1995), PRP = panretinal photocoagulation, NVD = neovascularization on the disk, NVE = neovascularization elsewhere in the retina, SVL = severe visual loss.

lar edema. Dyslipidemia leads to the development of hard exudates (Chew et al., 1996; Lyons et al., 2004). Clinical studies had shown the beneficial effects of lipid lowering agents such as atorvastatin and simvastatin in reducing hard exudates and progression of retinopathy (Harrold et al., 1969; Cullen et al., 1974).

## 5. Ocular managements of diabetic retinopathy

It may involve any or combination of laser, vitrectomy and/or pharmacological therapy. **Laser photocoagulation** is accomplished by directing a focused laser (**L**ight **A**mplification by the **S**timulated **E**mission of **R**adiation) beam of a discrete wavelength onto specified parts of the retina. Its absorption in a variety of intra-ocular pigmented retinal layers, causes a local rise in temperature which in turn causes denaturation of tissue proteins and coagulative necrosis. Laser treatment is used to treat diabetic macular edema either in the form of focal or grid using small spot size, short duration and low power enough to produce whitening of the retina. Focal treatment is required for focal lesions (e.g., microaneurysms, IRMA) located between 500 and 3000 μm from the center of the macula, which causes the hard exudates and retinal thickening. Photocoagulation may also be used in a form of a grid pattern sparing the fovea and the maculopapillary area to treat diffuse areas of leakage in the macula (Dowler, 2003; Mohamed et al., 2007). Panretinal photocoagulation (PRP) is indicated for the treatment of high-risk proliferative diabetic retinopathy and eyes with severe non-proliferative diabetic retinopathy and early proliferative diabetic retinopathy that are at high risk for progression or for poor outcome. Results of Diabetic Retinopathy study (DRS) (Anon., 1978; Shin et al., 2009; Diabetic Retinopathy Study Research Group, 1981) and the Early Treatment Diabetic Retinopathy Study (ETDRS) (Anon., 1991), have provided the strongest evidence to establish the place of panretinal photocoagulation as a standard technique for treating severe non-proliferative and proliferative diabetic retinopathy. Full PRP as used by DRS and ETDRS included 1200 or more 500 micron burns separated from each other by one half burn width at 0.1 s duration. It also had shown that panretinal photocoagulation reduces the risk of moderate and severe visual loss by 50% in patients with severe non-proliferative and proliferative retinopathy (Table 2). The aim of panretinal photocoagulation is to prevent the onset or induce the regression of neovascularization without vitreous hemorrhage or fibrovascular proliferation. This is done by destroying the ischemic peripheral retina with 1500–3000 burns that spare the disk, the macula and maculopapillary nerve bundle. It is done using enough power to produce a mild-to-moderate white burn, using shorter burn duration for patients comfort. This will result in concentrating the remaining retinal blood flow onto the macula and adjacent important areas. Laser photocoagulation is not without adverse effect. The adverse effects of PRP include visual field constriction, night blindness, color vision changes, accidental laser burn to macula.

## 6. Ocular pharmacotherapy

Advances in pharmacotherapy had shown encouraging promise in the treatment of diabetic retinopathy. (a) **VEGF inhibitors** are group of drugs that bind to VEGF receptors without causing its activation thus blocking new vessels formation and enhanced vessels permeability. Examples of these drugs include Pegaptanib, Ranibizumab, bevacizumab and Regeneron. They play an important role in the management of diabetic retinopathy and it was found to be safe in humans. Intravitreal injections of anti-VEGF drugs produce reductions in macular thickening, but on average the magnitudes of the reductions and the durations of responses are less than with intravitreal triamcinolone injections. This might suggest that other biochemical pathways not involving VEGF are important in the pathogenesis of diabetic macular edema (Roh et al., 2008; Arevalo et al., 2007; Do et al., 2009; Ozkiris, 2009; Querques et al., 2009; Adamis et al., 2006). **Pegaptanib** (Macugen) is a pegylated RNA an anti-VEGF that acts by targeting the 165 isoform of VEGF was approved for the treatment of neovascular age-related macular degeneration (AMD). It had also been shown to improve diabetic macular edema (Hornan et al., 2010; Macugen Diabetic Retinopathy Study Group, 2005) and cause regression of neovascularization in patients with proliferative diabetic retinopathy and help in cases with vitreous hemorrhages. **Ranibizumab** (Lucentis), is a recombinant humanized monoclonal antibody fragment with specificity for all isoforms of human VEGF-A. It had been approved for the treatment of neovascular age-related macular degeneration (Brown et al., 2006; Rosenfeld et al., 2006; Chun et al., 2006; Massin et al., 2010; Nguyen et al., 2009; Avery, 2006; Avery et al., 2006; Kook et al., 2009). It has also been found to be useful for diabetic macular edema. In the 2 years update READ2 study presented at the AAO Oct 2010; on the effect of ranibizumab for diabetic macular edema it improves visual acuity and reduces retinal thickness but repeated injection may be necessary. Combination with laser reduces the need for repeated injection. Restore study report after 12 months of ranibizumab in the treatment of macular edema revealed that ranibizumab alone is superior to laser monotherapy and combination of laser did not add much (AAO meeting Oct. 2010). **Bevacizumab** (Avastin) is a full-length humanized monoclonal antibody against all isoform of VEGF-A. It was found to effective for the treatment of neovascular age-related macular degeneration and for diabetic retinopathy (Avery, 2006; Avery et al., 2006; Kook et al., 2009; Scott et al., 2007; Spaide and Fisher, 2006; Rosenfeld, 2006; Karim and Tang, 2010; Arevalo et al., 2010; Gulkilik et al., 2010; di Lauro et al., 2010; Hernández-Da Mota and Nuñez-Solorio, 2010; Abdelhakim et al., 2010). It has been shown to be effective in minimizing the risk for post operative hemorrhage after vitrectomy (Saito et al., 2010; Brouzas et al., 2009; Hattori et al., 2010) and surgery for neovascular glaucoma (Wu et al., 2010; Parravano et al., 2009). Sometimes there is a need for repeating the intravitreal injections. However, the number of repeated injections is not settled. Avastin had been used in combination with triamcinolone at the end of vitrectomy for vitreous hemorrhage in patients with proliferative diabetic retinopathy with encouraging results. It is worth mentioning that intravitreal Avastin at the time of cataract surgery is effective in reducing diabetic macular edema post operatively (Fard et al., 2010). **VEGF Trap eye** (Regeneron) is S fusion protein specifically designed to bind all forms of VEGF-A. It had been shown that a single intravitreal injection of VEGF Trap-Eye was well tolerated and was effective in patients with diabetic macular edema.

The anti-VEGF drugs have lower side effect profile without the tendency to cause cataract and raise intra-ocular pressure as compared with steroid (Marticorena et al., 2010; Micieli et al., 2010). However; epiretinal membrane was reported after intravitreal Avastin for retinal vein occlusion and some systemic adverse effects were reported. In the review of 12,699 patients who received intravitreal Avastin: high blood pressure (0.46%), cerebrovascular accidents (0.21%) and myocardial infarction (0.19%) were reported. Whether these adverse effects related to the medicine or to the stress associated with the procedure remain unclear.

**Corticosteroids** are group of compounds which share three six membered carbon rings and one five membered carbon ring. The natural occurring members of this group are the sex hormones and the hormones of the adrenal glands. The synthetic members of this group are wide range of products used for therapeutic purposes with different potency (Table 3). They may produce their effects through multiple mechanisms of actions including their potent anti-inflammatory and VEGF regulating effects. They had been used in the treatment of diabetic retinopathy as peribulbar, sub-tenon and intravitreal injections. Peribulbar triamcinolone or methylprednisolone injections have been used to treat diabetic macular edema either as monotherapy or as adjunctive therapy to laser. Short-term efficacy in thinning the macula and improving visual acuity has been demonstrated but less effective than intravitreal. Intravitreal triamcinolone (IVTA) has shown significant improvements in diabetic macular edema and visual acuity in short term and it was found to be superior to sub-tenon injection (Jonas, 2007; Gillies et al., 2006; Massin et al., 2004; Dehghan et al., 2008; Audren et al., 2006; Avitabile et al., 2005; Wu et al., 2008; Yilmaz et al., 2009; Takata et al., 2010). The short term effect necessitates repeated intravitreal injections which was associated with some complications including steroid-induced elevation of intra-ocular pressure (IOP), crystalline maculopathy and steroid-induced cataract (Bursell et al., 1999; Yilmaz et al., 2009; Sarraf et al., 2010). To minimize the side effects lower dose of triamcinolone were studied, and it was found that intravitreal injection of 4 mg had better effect as compared with 1 mg injection but the complications were more with the higher dose. In a randomized clinical trial comparing serial intravitreal triamcinolone injection therapy using 1 or 4 mg to focal/grid photocoagulation, focal/grid photocoagulation showed superior efficacy and fewer side effects. A single injection of intravitreal of more potent steroid (dexamethasone 0.4 or 0.8 mg) did not have significant beneficial effects on diabetic macular edema within 3 months from injection (Chan et al., 2010). The use of slow release medications had gained increasing interest.

**Table 3** Relative potencies of corticosteroids (Katzung, 2004).

| Types | Potencies |
|---|---|
| Cortisone | 0.8 |
| Cortisol | 1 |
| Prednisone | 4 |
| Methylprednisolone | 5 |
| Triamcinolone | 5 |
| Betamethasone | 25 |
| Dexamethasone | 25 |
| Fluocinolone | 25 |

Liposomes are microscopic, spherical vesicles that form when hydrated phospholipids arrange themselves in circular sheets with consistent head–tail orientation. These sheets join each other to form a bilayer membrane that encloses some of the water and water-soluble materials (e.g., drugs) in a phospholipid sphere. Liposomes can be custom-designed for almost any need by varying the lipid contents, sizes, surface charges, and method of preparation. Alghadyan et al. had studied the effect and the half life of intravitreal injection of liposome with penicillin and cyclosporin in rabbits and found encouraging results (Alghadyan et al., 1988a–e). Recently intravitreal retinal implants had also been developed, allowing extended drug delivery. Implanted intravitreal fluocinolone acetonide was shown to be associated with improvement in visual acuity in diabetic macular edema (Pearson et al., 2006; Schwartz and Flynn, 2010). A sustained release drug delivery system for dexamethasone inserted trans-sclerally into the vitreous produced statistically significant visual acuity improvement for 90 days after insertion and was well tolerated for 180 days (Kuppermann et al., 2007). In Fame study 24 months report on the use of fluocinolone acetonide insert (Iluvein) in the treatment of diabetic macular edema was found to be of benefit in reducing the macular edema. Cataract and the glaucoma were reported as complications of the treatment (AAO meeting Oct. 2010). Similar results were found with Placid trial. Placid trial report in AAO Oct. 2010, reported the result of the use of Dexamethasone implant (Ozurdex) for the treatment of diabetic macular edema and they found that visual acuity improved with combination of dexamethasone with laser more than with laser alone. Still elevated IOP was one of the complications they faced.

Other pharmacotherapies in the management of diabetic retinopathy were suggested. Protein Kinase C (PKC) inhibitors such as Ruboxistaurin are expected to play a role in the management of diabetic retinopathy. The oral administration of this medication demonstrated a positive result in reducing macular edema (Aiello et al., 2006; Fabbro et al., 2000). Growth hormone inhibitors (somatostatin analogs) may inhibit angiogenesis directly through somatostatin receptors present on endothelial cells and indirectly through the inhibition of postreceptor signaling events of peptide growth factors such as insulin-like growth factor 1 and VEGF. It was found that Octreotide (growth hormone inhibitor) therapy for severe non-proliferative and early proliferative diabetic retinopathy retard the progression of the diabetic retinopathy (Grant et al., 2000). Short-term high-dose antioxidant therapy with oral vitamin E may help in normalizing retinal hemodynamics in diabetic patients (Kunisaki et al., 1995; Bursell and King, 1999; Bursell et al., 1999). The place of many potential pharmacotherapies in diabetic retinopathy such as Interferon-alpha 2a, acetazolamide, intravitreal injection of tissue plasminogen activator and pigment epithelium-derived factor needs to be evaluated. Intravitreal injections of erythropoietin in eyes with severe, chronic diabetic macular edema showed a short-term positive response (Li et al., 2010). Anti-tumor necrosis factor (TNF) infliximab (monoclonal antibody) also showed some benefit in the management of diabetic macular edema (Sfikakis et al., 2010).

Combination therapy had been used with some encouraging results. The use anti-VEGF therapy as an adjunct to the panretinal photocoagulation was found to be beneficial. Intravitreal bevacizumab or triamcinolone with macular photoco-

agulation were found to be superior than either one of the modalities alone in diabetic macular edema (Solaiman et al., 2010; Cho et al., 2010; Kang et al., 2006; Lam et al., 2007). There were some evidences suggesting that combined intravitreal and Peribulbar Triamcinolone and Focal Laser Therapy reduces macular thickening somewhat better. Intravitreal bevacizumab and triamcinolone as initial injection followed by two intravitreal bevacizumab injections given at 6-weeks intervals were no more effective in decreasing diabetic macular than three consecutive intravitreal injections of bevacizumab given at 6-week intervals (Soheilian et al., 2007). In Diabetic Retinopathy Clinical Research (DRCR) network reported at the AAO Oct 2010 the result on: (1) intravitreal ranibizumab with or without laser in treatment of diabetic macular edema and they found that the combination is than the laser alone; (2) intravitreal triamcinolone with or without laser and they found that the combination is not superior to laser alone; (3) they recommended that ranibizumab with laser should be considered for the treatment of Diabetic retinopathy.

**Surgical management** may involve less invasive procedures such as laser, intravitreal injection of medications or gas or more invasive procedures such as vitrectomy. Laser (argon, krypton, or Nd:YAG) may be used to create an opening in the posterior hyaloid face to aid in the breakthrough of subhyaloid hemorrhage into the vitreous cavity to move it away from the fovea. Intravitreal gas (SF6) injection can also resolve subhyaloid hemorrhage through the induction of a posterior vitreous detachment (Chung et al., 2008; Raymond, 1995; Park and Seo, 2004; Nasrallah et al., 1988). The indications for vitrectomy in diabetics include: (1) vitreous hemorrhage (final visual result is dependent on the status of the macula), (2) traction retinal detachment (best results if vitrectomy is performed soon after macular involvement or when macula is threatened), (3) combined traction–rhegmatogenous retinal detachment (vitrectomy with silicone oil tamponade yields fairly good results), (4) severe fibrovascular proliferation (important to apply extensive PRP prior to vitrectomy, if possible), (5) postvitrectomy fibrinoid syndrome (best managed with adjunctive medication), (6) anterior hyaloidal fibrovascular proliferation (poor prognosis, therefore, best prevented with appropriate anterior retinopexy in high-risk eyes). Early vitrectomy has been shown to improve visual recovery in patients with proliferative diabetic retinopathy and severe vitreous hemorrhage. The Diabetic Retinopathy Vitrectomy Study Research Group (1985, 1988a,b) (Table 2) evaluated the risks and the benefits of early surgical intervention versus conventional treatment for vitreous hemorrhage and very severe PDR. The results of DRVS demonstrated that patients who underwent early vitreoretinal surgery had better outcome than those treated conservatively, with 25% of the early vitrectomy group versus 15% of the observation group having 20/40 or greater vision after 2 years' follow-up. Eyes with diabetic macular edema (DME) have a lower prevalence of posterior vitreous detachment than eyes without DME (Nasrallah et al., 1988). The observation that resolution of DME after posterior vitreous detachment suggested that surgical induction of a vitreomacular separation might improve diabetic macular edema (Hikichi et al., 1997). Intravitreal ovine hyaluronidase injection and autologous plasmin enzyme were found to induce vitreolysis and posterior vitreous detachment and subsequent resolution of diabetic macular edema. Vitrectomy including removal of posterior hyaloid for diabetic macular edema was found to be of benefit (Recchia et al., 2005; Patel et al., 2006a,b; Pendergast et al., 2000; Rosenblatt et al., 2005; Stolba et al., 2005; Harbour et al., 1996; Kumagai et al., 2009) In refractory macular edema vitrectomy can be used for eyes with a stretched posterior hyaloid adherent to the macula, and for eyes with persistent diabetic macular edema despite previous focal laser or intravitreal triamcinolone injection. Vitrectomy has a potential to be a primary therapy in eyes with more severe edema and greater visual acuity loss at presentation.

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