Ann Natl Acad Med Sci (India), **46(2):** 98-117, 2010

Clinical Characteristics, Diagnosis and Management of Diabetic Retinopathy

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Abstract

Diabetic retinopathy is a major health problem in patients with diabetes world over. During the past 15 years, improvements in the medical management of diabetes have led to a decrease in both the onset and progression of diabetic retinopathy. However, there is still no proven intervention that prevents or reverses visual loss from diabetic macular edema. The present review outlines the magnitude of the problem in India, the risk factors for diabetic retinopathy, pathophysiology of lesions developing in diabetic retinopathy and their clinical characteristics. This is followed by a summary of conventional and current strategies to manage the potentially blinding complications of diabetes mellitus.

Keywords: diabetic retinopathy, diabetic macular edema

Diabetes mellitus (DM) is one of the leading causes of blindness in the Western countries, accounting for nearly 10 % of all new cases of legal blindness in the patients between the ages of 45 and 74 (1,2,3). In the Indian subcontinent, only limited data are available on the prevalence of diabetic retinopathy (DR) in the general population. Studies from South India have reported prevalence rates of DR in type 2 DM patients varying from 12 %-37 % (4-10). A hospital-based study from North India reported a higher (28.9%) prevalence of DR in type 2 DM (11).

According to the World Health Organization, India will become one of the major hubs of diabetic population during the next 2 decades; the number of cases of adult-onset DM will grow to

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nearly 80 million in 2030 from 18 million in 1995 (12).

RISK FACTORS FOR DIABETIC RETINOPATHY

1. *Duration of diabetes*

The duration of diabetes is the strongest predictor for DR (8). A direct correlation between frequency and severity of DR and the duration of diabetes is well known (8,11,13,14), with the duration of disease being the best predictor of DR. Those who have duration of diabetes of more than 15 years have a 6.43-times risk of developing retinopathy in comparison with those whose diabetes is newly detected (8).

2. *Type of diabetes*

The prevalence of retinopathy at diagnosis of Type 2 DM is much greater than the prevalence at diagnosis of Type 1 diabetes. The prevalence of retinopathy in Type 1 diabetes at diagnosis is between 0% and 3% whereas it is 6.7% to 30.2% in patients with Type 2 diabetes (15). This difference is largely because Type 2 DM remains undiagnosed for number of years after the onset.

Type 1 DM: These patients do not develop DR for 5 years after the initial diagnosis. Proliferative diabetic retinopathy (PDR) is very uncommon before 15 years of duration but after 20 years, 50% of these patients would develop PDR. Proliferative DR is more common in type 1 than in type 2 DM.

Type 2 DM: In these patients, the time of onset and therefore duration are difficult to predict precisely and approximately 3-4% of these patients would have changes of PDR at time of presentation. The prevalence of PDR after 20 years of onset is expected to be only 5-10% i.e. much less than that of type 1 DM (Table 1).

Table 1: Prevalence of PDR

Types of diabetes	Duration of disease in years		
	0-5 yr	10 yr	20 yrs
Type 1	-	4%	50%
Type 2	3-4%	10%	5-10%

3. *Age and Sex*

The prevalence and severity of DR increases with increasing age in type 1 DM but not in type 2 DM (8, 16). DR is reported to be more common in men (6-8) but the exact reason for male preponderance has not been determined.

4. *Type of treatment*

Those who take insulin have a higher risk of retinopathy developing or progressing compared with those who do not (8,17).

5. *Metabolic control*

Hyperglycemia is the most important risk factor for the development of DR. The two large multicentric trials-Diabetic Control and Complications Trial (DCCT) and Early Treatment of Diabetic Retinopathy Study (ETDRS) have shown that intensive treatment of diabetes delays the onset and reduces the progression of DR in both types 1 and 2 DM (17). A strong association between HbA1c level and DR has also been observed (11,17).

6. *Hypertension*

Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) and United Kingdom Prospective Diabetes Study (UKPDS) suggest that hypertension increases the risk and progression of DR and macular edema. In UKPDS, tight control of blood pressure resulted in 34% reduction in progression of retinopathy with 47% reduced risk of deterioration in visual acuity of three lines (18).

7. *Nephropathy*

The prevalence of PDR is much higher in patients with persistent microalbuminuria (19,20). A diabetic patient with retinopathy is at a moderate risk of having nephropathy, and a patient with nephropathy is at a much higher risk of developing retinopathy.

8. *Dyslipidemia*

In the ETDRS, elevation of serum cholesterol and triglycerides was associated with risk of retinopathy (21). We reported reduction in edema, severity of hard exudates and subfoveal lipid migration in patients with type 2 DM and dyslipidemia, using a lipid-lowering drug, atorvastatin, as an adjunct to macular photocoagulation (22).

9. *Anemia*

In ETDRS, an increased risk of retinopathy was found in patients with the hemoglobin level of less than 12 g/dl (23).

10. *Neuropathy*

Patients with neuropathy have more retinopathy (23).

11. *Pregnancy*

Pregnancy in type 1 diabetic women is associated with risk of development and worsening of retinopathy but is not associated with post-partum worsening of retinopathy (24). The factors associated with its progression include the pregnant state itself, duration of diabetes, amount of retinopathy at conception, blood glucose control, and the presence of coexisting hypertension (25).

12. *Puberty*

In WESDR, younger onset subjects who were post-menarchal stood a 3.2 times greater risk of developing DR as compared to pre-menarchal subjects (26).

13. *Genetics*

Data from the WESDR and the DCCT have suggested the possibility of genetic predisposition to microvascular complications of diabetes including diabetic retinopathy.

PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

DR results from a combination of systemic and ocular abnormalities. It is essentially a microangiopathy affecting mainly small caliber retinal vessels (i.e. precapillary arterioles, capillaries and venules) eventually resulting in either microvascular occlusion or microvascular leakage. There are three important structural vascular changes, namely, (1) pericyte degeneration, (2) basement membrane thickening and (3) endothelial cell proliferation.

The first structural change caused by hyperglycemia is thickening of the microvascular basement membranes associated with loss of pericytes resulting from various biochemical alternations, hemodynamic and endocrine factors (27). The loss of retinal capillary pericytes is one of the earliest histological lesions of DR. This results in abnormal autoregulation that interferes with normal blood flow. In addition to resulting in breakdown of capillary integrity, the pericyte death leads to a loss of control over endothelial cell proliferation.

Clinical course

The entire disease spectrum in DR can be classified as:

1. Non-proliferative/background DR
   a. Mild
   b. Moderate
   c. Severe
2. Proliferative DR
3. Advanced disease
   a. Tractional/combined retinal detachment
   b. Persistent vitreous hemorrhage
   c. Neovascular glaucoma

Non-proliferative DR/background DR (NPDR/BDR)

DR begins as non-proliferative abnormalities and progresses to PDR. Macular edema can develop at any time in the progression of DR. Macular ischemia, retinal and vitreous hemorrhage, and retinal detachment are the primary causes of blindness in patients with DR.

NPDR constitutes the intraretinal abnormalities, which precede and also accompany the proliferative changes developing in front of the retina or within the vitreous cavity. The term non-proliferative retinopathy has replaced previously used term 'background retinopathy'. The disease is characterized by:

1. *Capillary closure:* The earliest detectable vessel closure in DR occurs at the level of capillary bed. Microaneurysms form as a response to focal capillary closure as these tend to cluster around small areas of capillary non-perfusion.
2. *Microaneurysms:* These are focal saccular dilations of the retinal capillary bed in both superficial and deep retinal capillary beds, located predominantly within the inner nuclear layer on capillaries linking the superficial and deep capillary networks. More microaneurysms are revealed by fundus fluorescein angiography (FFA) than by ophthalmoscopy. An FFA also differentiates microaneurysms from dot or blot hemorrhages.
3. *Retinal hemorrhages:* Hemorrhages assume several morphologic forms, depending on the depth within the retina. ETDRS defines a hemorrhage as a red spot that is more than 1/12 the diameter of an average optic disc or 125 μm in its longest dimension and has irregular margins and/or uneven density. Retinal hemorrhages are significant because their severity represents the severity of background retinopathy in general. Generally, intraretinal hemorrhages do not cause any visual disturbances unless there is foveolar hemorrhage, which can cause decreased visual acuity. These hemorrhages usually resolve over a period of 6 weeks to 3 months whereas a few larger ones take longer.
4. *Hard exudates:* Hard exudates are extracellular accumulation of lipids derived from leakage of serum from abnormal vessels. These are small white or yellowish white deposits with sharp margins. They often have a slightly waxy or glistening appearance and are usually located in the outer plexiform layer of the retina. They get reabsorbed by a process of phagocytosis and thus disappear over a period of months to years but visual acuity may remain poor because of permanent retinal damage.

5. *Macular edema:* Diabetic macular edema (DME) is the most important cause of moderate visual loss in patients with DR (28). The edema is caused primarily by a breakdown of the inner blood retinal barrier resulting in leakage of fluid and plasma constituents from abnormally permeable micro-aneurysms, intra-retinal micro-vascular abnormalitites (IRMA) and dilated or normal caliber retinal capillaries. It may be focal or diffuse.

Focal macular edema is characterized by area of focal leakage from specific capillary lesions, microaneurysms and dilated capillary segments. These focal areas of edema are often delineated from adjacent healthy area by complete or partial rings of hard exudates. The excess fluid is transported into intravascular compartment by the adjacent healthy capillaries that are incapable of allowing macromolecules to pass through. Thus, the so-called circinate ring of hard exudates marks the outer limit of focal macular edema.

Diffuse macular edema: Diffuse leakage occurs from the generally dilated capillary bed throughout the posterior retina, usually not associated with hard exudates. This is because the diffuse breakdown of the inner blood retinal barrier allows the passage of smaller molecules, like water but not of lipoproteins. Cystoid spaces develop more commonly in diffuse macular edema and are uncommon in focal macular edema. These cystoid spaces may be visible clinically, but are better seen in late phase of FFA when the fluorescein dye pools in these cystoid spaces. Certain systemic factors may be associated with the exacerbation and amelioration of diffuse macular edema, which include cardiovascular, renal diseases and systemic hypertension. On FFA, diffuse macular edema is characterized by enhanced visibility of the dilated capillary bed throughout the posterior pole along with widening of inter-capillary spaces and the extravasation of dye leading to increased hyperfluorescence seen in the late phase.

ETDRS has defined macular edema and clinically significant macular edema (CSME) separately (figure 1). It is important to categorize whether the patient has CSME or not because as per ETDRS protocol, patients without CSME do not require treatment. ETDRS defined CSME as:

1. Retinal thickening at or within 500 μm of the center of the macula and/ or

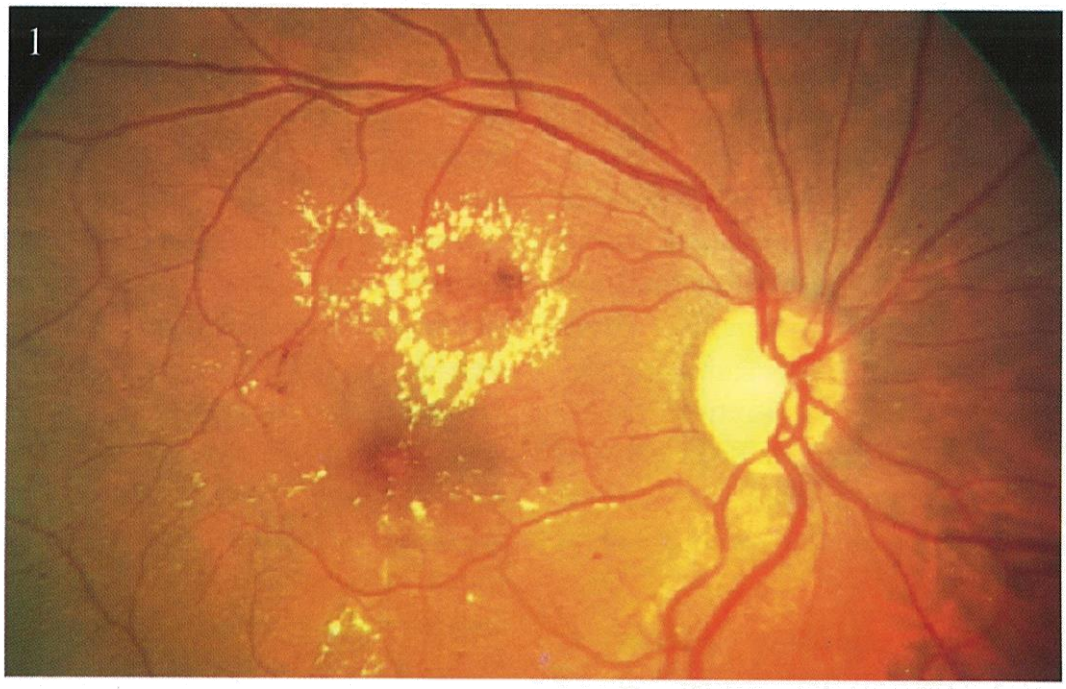

Figure 1: Fundus photograph of right eye with non-proliferative diabetic retinopathy showing dot and blot hemorrhages with circinate retinopathy corresponding to clinically significant macular edema.

2. Hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina and/or
3. Zone(s) of retinal thickening at least one disc area in size, part of which is within one disc diameter of the center.

Pre-proliferative DR (PPDR)/ Moderate-severe non-proliferative DR

This is an intermediate stage between NPDR and PDR. In PPDR, there are increasing signs of ischemia secondary to precapillary arteriolar occlusion, clinically manifesting as soft exudates, venous beading and loops, intraretinal microvascular abnormalities (IRMA) and widespread areas of capillary non-perfusion. ETDRS has categorized these features of soft exudates, venous changes and IRMAS as severe NPDR.

1. *Soft exudates:* Soft exudates, also called cotton wool spots, are localized superficial swellings in the nerve fiber layer developing

from retinal axonal swelling due to accumulations of intracellular fluid or organelles due to impaired axoplasmic flow in the area of non-perfusion. These are round or oval in shape, pale yellow-white or grayish-white in color with fluffy appearance, feathery edges and frequently with striations parallel to the nerve fibers. Soft exudates occur most often near the optic disc, where axon are most numerous. The presence of cotton wool spots does not always indicate an increase likelihood of progression to PDR.

2. *Venous beading and loops:* The localized variation in venous caliber is typical of DR and is designated beading. Venous loops are hairpin or semicircular deviations of the vein from its normal course. Reduplication of vein or apparent doubling of the vein over a short segment is perhaps related to partial obstruction of the original vein. Severe venous dilatation, with beading, reduplication and abnormal loop formation are seen in areas of capillary non-perfusion, thus indicating ischemia. These serve as warning signs of future PDR.
3. *IRMA:* These are narrow, tortuous, intraretinal vascular segments representing either dilated retinal capillaries and/or intraretinal new vessels. These may represent intraretinal neovascularization. The term IRMA, however, is only descriptive. Presence of IRMAs is a sign of retinal ischemia.
4. *Severe capillary occlusion and featureless retina:* In the later stages, larger arterioles may also occlude completely resulting in extensive areas of capillary non-perfusion. The arterioles appear white thread like without small vessel branching. The retina appears thin and atrophic and there is absence of background lesions. This could mislead the examiner in underestimating the actual severity of the disease. The FFA reveals extensive areas of capillary non-perfusion.

Proliferative DR (PDR)

It is defined as the presence of newly formed blood vessels and/or fibrous tissue arising from the retina or optic disc, extending along posterior hyaloid surface.

1. *Neovascularisation:* The most important factor triggering the

development of the new vessels is ischemia of the inner retinal layers which stimulates the production of angiogenic factors, namely, Vascular Endothelial Growth Factor (VEGF) which act locally, diffuse through the vitreous to other areas of the retina, to the optic disc and also into the anterior chamber. These new vessels proceed through characteristic cycle of proliferation followed by either partial or complete regression or posterior vitreous detachment. These may be found on the optic disc or elsewhere on the retina (figures 2 and 3). The proliferating new vessels tend to grow between the internal limiting membrane and the posterior hyaloid face, which acts as scaffold for these growing vessels.

2. *Subhyaloid bleed / Vitreous hemorrhage:* Blood may collect in the fluid vitreous posterior to the detached vitreous, which generally absorbs within weeks or several months (figure 4). Hemorrhage in the formed vitreous is, however, very slow to absorb and may take several months.

3. *Traction Retinal Detachment:* As the vitreous contracts, it might pull underlying retina anteriorly, towards the vitreous base, resulting in development of retinal detachment

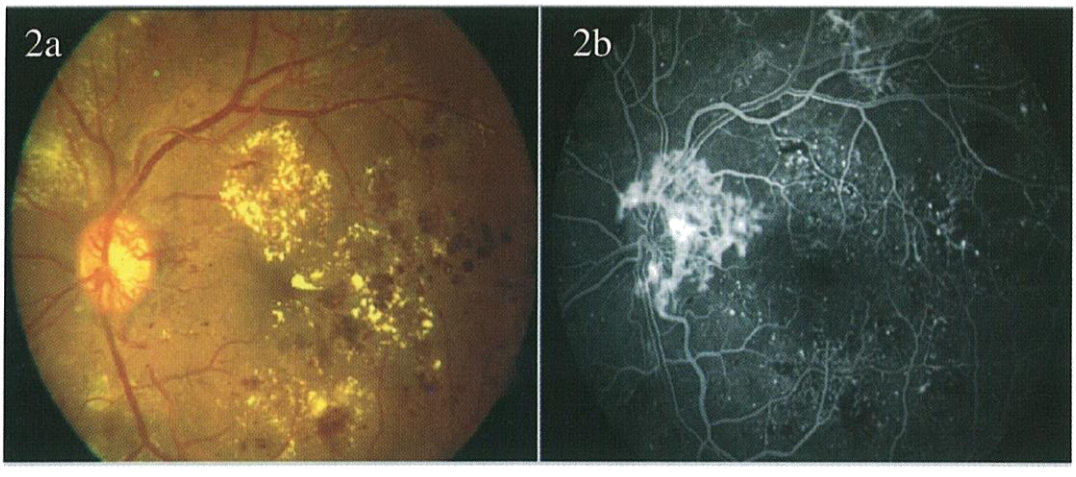

Figure 2 a and b: Left eye showing neovascularization on the optic disc, clinically significant macular edema on the fundus photograph (a), along with leaking microaneurysms on Fundus fluorescein angiography (b).

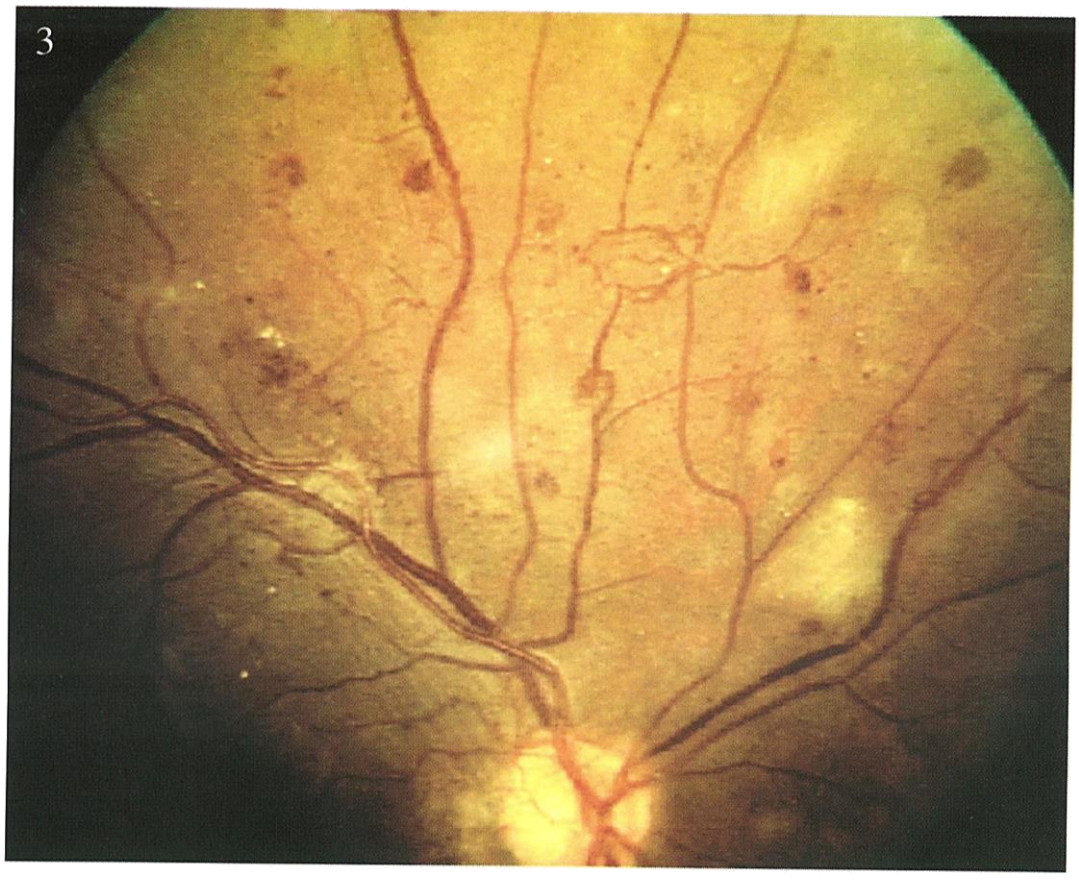

Figure 3: Fundus photograph of right eye showing neovascularization elsewhere on the retina.

with a typical concave shape (figure 5). Sometimes, small full thickness holes may develop near the proliferations, thus, leading to development of rhegmatogenous detachment.

DIAGNOSIS AND ANCILLARY INVESTIGATIONS

The diagnosis of DR is essentially clinical. Several ancillary investigations are needed to aid the diagnosis, plan the treatment and monitor the response to treatment. These include fundus photographs (stereoscopic), FFA mainly to detect and classify DME, and Optical Coherence Tomography (OCT) in DME for assessing the presence of taut posterior hyaloid membrane.

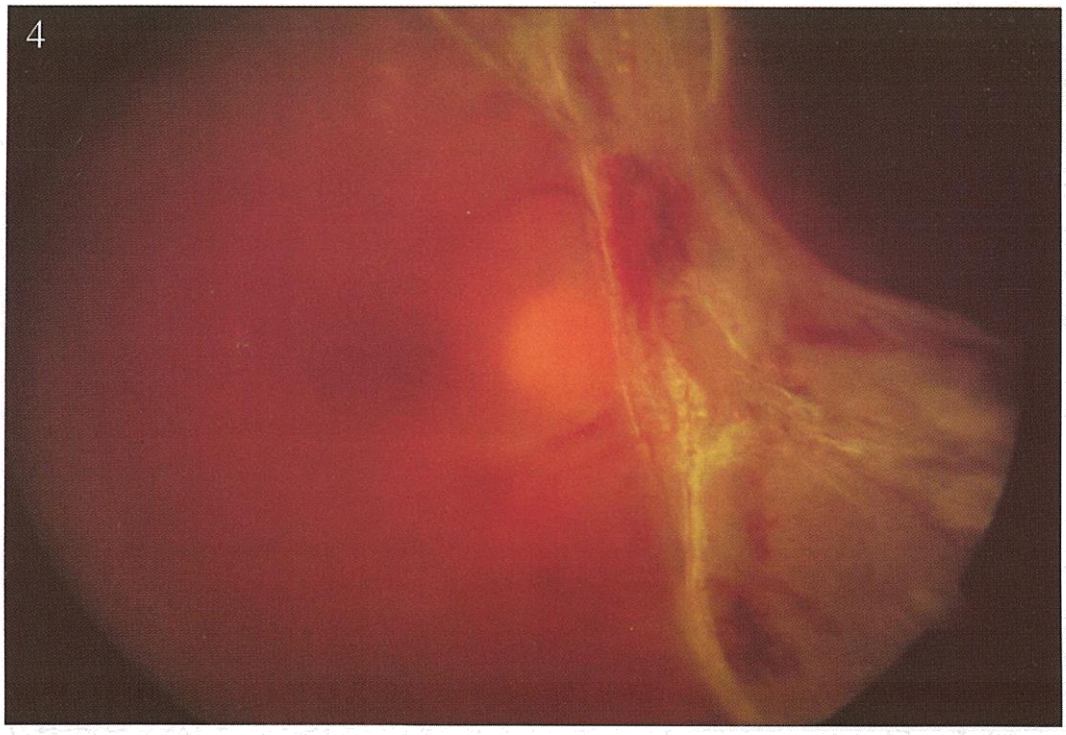

Figure 4: Fundus photograph of right eye showing subhyaloid hemorrhage with extensive fibrovascular proliferation.

MANAGEMENT

Since DM has multifactorial origin, an optimal metabolic control of hyperglycemia, HbA1c levels, hypertension, dyslipidemia, anemia and nephropathy should be an important treatment goal.

DME

Medical management of DME includes systemic control of risk factors combined with local treatment that includes laser photocoagulation and pharmacological agents including corticosteroids, anti-VEGF agents, Protein Kinase C inhibitors, Small interfering RNA (siRNA) molecules and Aldose Reductase Inhibitors (ARIs).

Diffuse DME and macular edema with prominent cystoid changes are known to have a better response to pharmacological agents, while a focal DME responds better to laser treatment (29). We have observed better visual outcome with multifactorial interventions in DME before laser

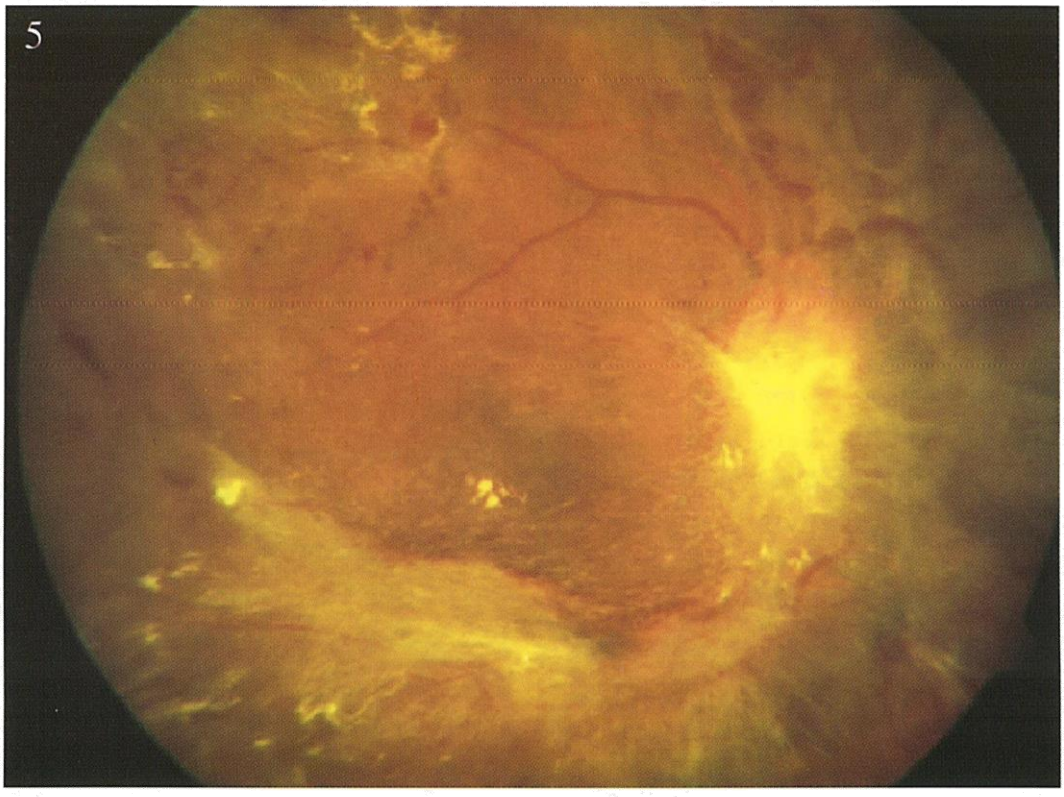

Figure 5: Fundus photograph of right eye showing extensive tractional retinal detachment over the posterior pole.

photocoagulation than is obtainable by the conventional strategies of laser photocoagulation, without enforcing systemic control (30, 31).

Laser photocoagulation

The ETDRS treatment technique of laser photocoagulation for CSME is currently the standard of care and can be divided into focal or grid laser. Ideally, the laser treatment is guided by the FFA for precise identification and treatment of lesions. The dimensions of the laser spots vary between 50 μm-100 μm in diameter and the exposure time is 0.05-0.1 second duration.In the focal laser photocoagulation, all focal leaks located between 500 μm to 3000 μm from the centre are treated directly.

During focal treatment, the laser directly targets the angiographically leaking microaneurysms. The treatable lesions are focal leaks situated more than 500 or within 300-500 μm from the center of macula causing retinal

thickening or hard exudates. Grid treatment is applied to the areas of thickened retina with diffuse leakage or capillary nonperfusion. Modified grid laser combines direct laser to focal leaks and grid to coexisting areas of diffuse leakage or non-perfusion In the grid laser photocoagulation, all areas of diffuse leakage extending within the arcade are treated with 50 – 200 μm spot size placed one burn width apart, at 0.1 second duration. The laser burns must be at least 500 μm away from the foveal center and 500 μm away from the disc margins. Avascular zones, other than the normal avascular foveal zone are also treated. The green wavelength (Argon, FD-Nd:YAG) is better absorbed by the hemoglobin and hence ideal for focal or grid laser photocoagulation (32).

The goal of macular laser photocoagulation for DME is to limit vascular leakage through focal laser burns of leaking microaneurysms or grid laser burns in areas of diffuse breakdown of the blood-retinal barrier. In the ETDRS, laser photocoagulation reduced the risk of vision loss by 50% in patients with CSME.

Patients with coexistent PDR with CSME need concomitant panretinal photocoagulation (PRP) that in turn can worsen the macular edema. The focal or grid photocoagulation is done first and PRP initiated in the nasal quadrant in the same sitting. The rest of the PRP can be completed in subsequent visits.

Argon green (514.4 nm) and frequency doubled Nd: YAG lasers (532 nm) are the lasers of choice in the management of DME. Over the following few weeks to months, after the closure of leakage areas, the excess fluid begins to reabsorb into the surrounding tissues and eventually the hard exudates are absorbed.

A repeat FFA is done at 3 months after laser photocoagulation for any persisting focal or diffuse leakage. Most patients need 1 to 3 sessions. DME requiring more than 3 treatments becomes recalcitrant and require alternative treatment with pharmacological agents.

Laser photocoagulation for PDR: Full or mild scatter PRP used in the ETDRS to treat severe NPDR and early PDR. The full scatter technique was similar to that employed in the DRS and consisted of applying 800 to 1600 burns, 500 microns in size, spaced half to one burn-width apart, extending from the optic disc to the equator. A new type of scanning laser i.e. Patterned scanning laser photocoagulation (PASCAL) is capable of giving multiple spots with a single foot pedal depression. Full scatter

treatment for PDR results in partial or complete regression of retinal and disc neovascularization. The DRS found that such treatment prevented severe visual loss by over 50% at 2 and at 4 years of follow up. When eyes with high-risk factors were considered, severe visual loss was found in 11% treated eyes and in 26% untreated controls. The visual benefit was apparent from 16 months of the study, lasted throughout the study period, and was sustained for several years after the study.

Pharmacotherapy

Despite the presence of current treatment strategies of DME, vision loss due to DME still occurs at an alarming rate. Laser photocoagulation is a late and destructive treatment that does not take the etiology of disease into account. Most of the diabetes related complications in the eye, like macular edema and neovascularization, occur secondary to the release of the growth factors in response to retinal ischemia.

Corticosteroids: Corticosteroids, in the form of intravitreal or posterior subtenon injections of triamcinolone acetonide are used for temporary reduction of DME before laser treatment. They are administered in the presence of macular edema refractory to laser treatment, heavy leakage in close proximity to fovea, high-risk characteristics of PDR or cataract making laser treatment more difficult. They have been demonstrated to inhibit the expression of the VEGF gene by the pro-inflammatory mediators, Platelet-derived growth factor (PDGF) and platelet-activating factor (PAF) in a time and dose-dependent manner. Steroids also have anti-angiogenic properties possibly due to inhibition of the expression of VEGF gene. However, the side effects of intravitreal corticosteroid injections, namely, rise in intraocular pressure and cataract formation needs to be carefully monitored.

Anti-VEGF agents: Among the anti-VEGF drugs, pegaptanib (Macugen; OSI Pharmaceuticals, Melville, NY), ranibizumab (Lucentis; Genentech Inc, South San Francisco, CA), bevacizumab (Avastin; Genentech Inc, South San Francisco, CA) and VEGF Trap (Regeneron Inc, Tarrytown, NY) inhibit the VEGF protein directly. Other drugs inhibit VEGF RNA such as bevasiranib (Opko Health Inc, Miami, FL) or inhibit molecules further upstream of VEGF such as rapamycin (Sirolimus, MacuSight Inc, Union City, CA) (33). Human clinical studies have shown favorable results in DME with the use of intravitreal anti-VEGF agents, pegaptanib sodium, ranibizumab

(Leucentis) and bevacizumab (Avastin) (34-37).

Protein kinase C inhibitors: Ruboxistaurin, an orally administered selective protein kinase C b-inhibitor, has been associated with a reduction of macular edema in eyes with DME (38).

Small interfering RNA (siRNA) molecules: Bevasiranib, the first siRNA molecules to enter clinical trials, is designed to inactivate VEGF mRNA and essentially silence the genes responsible for production of all VEGF isoforms (39).

Aldose Reductase Inhibitors (ARIs): The ARIs such as sorbinil, ponalrestat and tolrestat, have shown decrease in capillary cell death, microaneurysm count and fluorescein leakage (40). However, clinical trials of ARI had little therapeutic success and these are currently not in use.

Novel emerging drugs should enable better anatomical and functional outcomes for therapy of sight-threatening DME. As there is no proven intervention that prevents or reverses visual loss from DME, there is clearly a growing need for new and more effective modalities for treating DME.

Pars plana vitreous surgery

The major indications are non-clearing vitreous hemorrhage, macula-threatening traction retinal detachment (figures 4 and 5), and combined traction-rhegmatogenous detachment. Less common indications are macular edema with a thickened and taut posterior hyaloid, macular heterotropia, epiretinal membrane, and severe premacular hemorrhage and neovascular glaucoma. An OCT helps in differentiating tractional and non- tractional causes of DME.

The surgical treatment objective in these eyes includes clearing the media, relieving all anterior-posterior and tangential traction using delamination, segmentation or en-bloc techniques and performing adequate PRP to prevent development of subsequent iris neovascularisation (figure 6). The poor prognostic factors include tabletop detachments, absence of prior PRP and extensive fibrovascular proliferation.

SCREENING FOR DIABETIC RETINOPATHY

Ophthalmoscopy: Ophthalmoscopy is the most commonly used technique to screen for DR. When performed by an ophthalmologist, the specificity of direct and indirect ophthalmoscopy is high, but the sensitivity is low (34-50%), particularly for early retinopathy, in comparison to 7-field stereo photographic assessment.

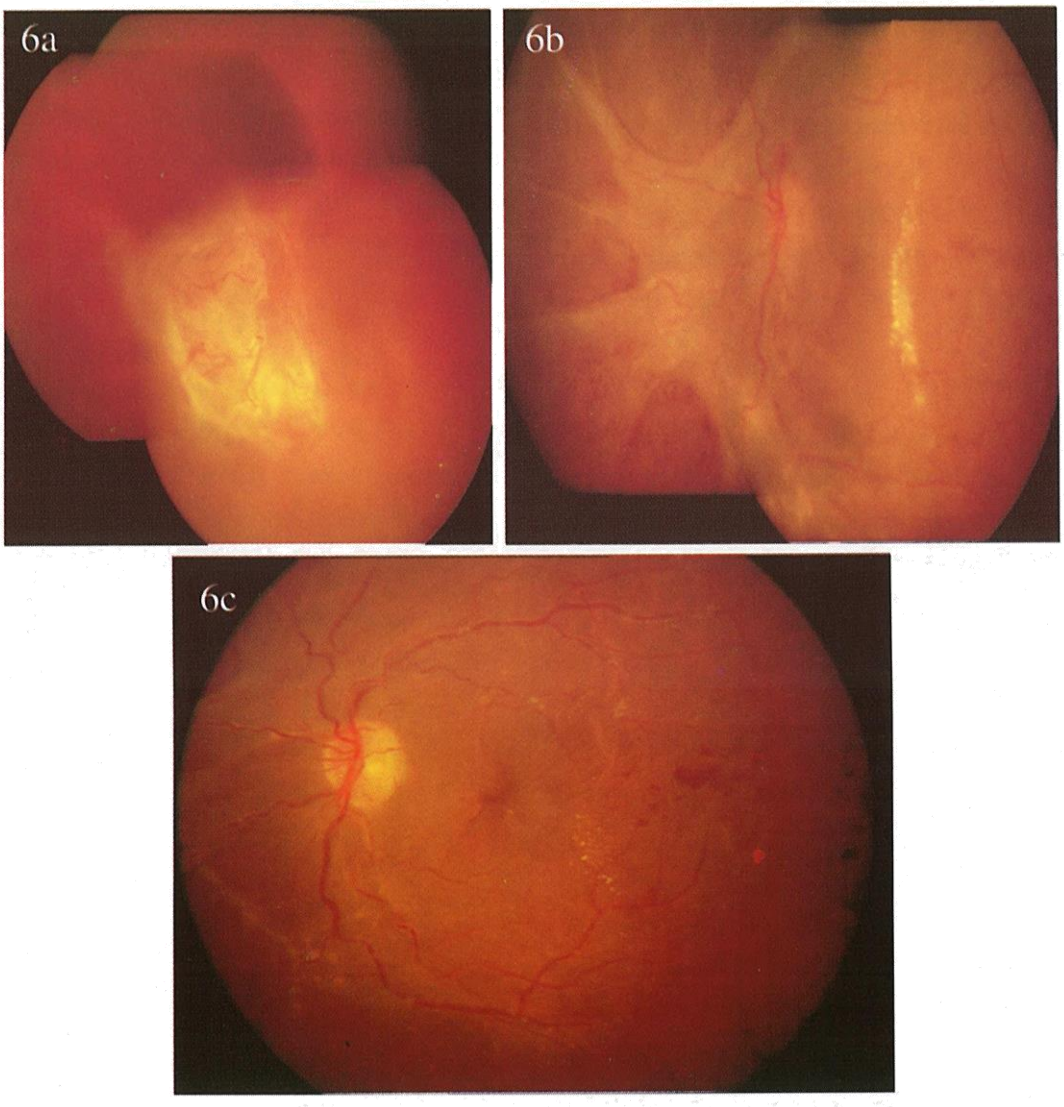

Figure 6: Fundus photograph of left eye showing massive fibrovascular proliferation with vitreous hemorrhage (a), peripapillary tractional retinal detachment (b), and the same eye following pars plana vitreous surgery (c).

***Digital imaging*:** Digital imaging makes fundus photography easier and more widely accessible. It may be used to obtain fundus images through non-dilated pupils. Mydriasis is usually necessary in older patients and dark irides. Single-field fundus photography with interpretation by trained readers

could serve as a screening tool to identify patients with diabetic retinopathy.

Tele- screening: A major advantage of digital technologies is the ability to transmit images to a centralized reading centre for grading. Implementing retinal imaging technology in a primary care setting results in significant increase in the rate of DR surveillance and in the rate of laser treatment for DR. However, tele-ophthalmology at present is not a substitute for comprehensive eye examinations.

References:

1. Benson WE, Brown GC, Tasman W eds. (1988). Diabetes and its ocular complications. W.B Saunders Company, Philadelphia, 1-5.
2. Gupta,V, Gupta A, Dogra MR, Singh R (eds) (2006). Diabetic Retinopathy: An Atlas and Text. Jaypee Brothers, New Delhi.
3. Klein R, Klein BEK, Moss SE, Linton KLP (1992). The Beaver Dam Eye study. Retinopathy in adults with newly discovered and previously diagnosed diabetes mellitus. *Ophthalmology* **99:**58-62.
4. Rema M, Ponnaiya M, Mohan V. (1996). Prevalence of retinopathy in non insulin dependent diabetes mellitus at a diabetes centre in Southern India. *Diabetes Res Clin Pract* **34:**29-36.
5. Sharma RA. (1996) Diabetic eye disease in southern India. *Community Eye Health* **9:**56-8.
6. Dandona L, Dandona R, Naduvilath TJ (1999). Population based assessment of diabetic retinopathy in an urban population in southern India. *Br J Ophthalmol* **83:**937-40.
7. Rema M, Premkumar S, Anitha B. (2005). Prevalence of diabetic retinopathy in urban India: The Chennai Urban Rural Epidemiology Study (CURES) eye study. *Invest Ophthalmol Vis Sci* **46:**2328-33.
8. Raman R, Rani PK, Reddi Rachepalle S, Gnanamoorthy P, Uthra S, Kumaramanickavel G, *et al.* (2009). Prevalence of diabetic retinopathy in India: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study Report 2. *Ophthalmology* **116:**311-318.
9. Ramachandran A, Snehalatha C, Vijay V, King H (2002). Impact of poverty on the prevalence of diabetes and its complications in

urban southern India. *Diabet Med* **19:**130-5.

10. Narendran V, John RK, Raghuram A, Ravindran RD, Nirmalan PK, Thulasiraj RD (2002). Diabetic retinopathy among self reported diabetics in southern India: a population based assessment. *Br J Ophthalmol* **86:**1014-8.
11. Agrawal RP, Ranka M, Beniwal R, Gothwal SR, Jain GC, Kochar DK, *et al.* (2003). Prevalence of diabetic retinopathy in Type 2 diabetes in relation to risk factors: Hospital based study. *Int J Diab Dev Countries* **23:**16-19.
12. Wild S, Roglic G, Green A, Sicree R, King H (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* **27:**1047–53.
13. Burditt AF, Caird FI, Draper GJ (1968). The natural history of diabetic retinopathy. *Q J Med* **37:** 303-17.
14. Kohner EM, Mcleod D Marshall J (1982). Diabetic eye disease. In: Complications of Diabetes. Keen H, Jarett RJ (eds), Edward Arnold, London, 19-108.
15. Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach Al (2004). Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye* **18:**963-983.
16. Klein R, Klein BE, Moss SE (1984). The Wisconsin Epidemiologic Study of Diabetic Retinopathy, II: Prevalence and high risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* **102:**520-6.
17. Roysarkar TK, Gupta A, Dash RJ, Dogra MR (1993). Effect of insulin therapy on progression of retinopathy in noninsulin-dependent diabetes mellitus. *Am J Ophthalmol* **15:**569-574.
18. Kohner EM, Aldington SJ, Stratton IM (1998). United Kingdom Prospective Diabetes Study, 30: Diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. *Arch Ophthalmol* **116:**297-303.
19. EDIC research group (2000). Retinopathy and nephropathy in type 1 diabetes patients four years after trial of intensive therapy. *N Engl J Med* **342:**381-9.
20. Mathiesen ER, Ronn B, Storm B (1995). The natural course of microalbuminuria in insulin-dependent diabetes: A 10-year

prospective study. *Diabetes Med* **12:**482-7.

21. Ferris FL III, Chew EY, Hoogwerf BJ (1996). Serum lipids and diabetic retinopathy. Early Treatment Diabetic Retinopathy Study Research Group. *Diab Care* **19:**1291-1293.
22. Gupta A, Gupta V, Thapar S, Bhansali A (2004). Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. *Am J Ophthalmol* **137:**675-82.
23. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, *et al.* (1998). Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. *Invest Ophthalmol Vis Sci* **39:**233-252.
24. Arun CS, Taylor R (2008). Influence of pregnancy on long-term progression of retinopathy in patients with type 1 diabetes. *Diabetologia* **51:**1041-1045.
25. Sheth BP (2008). Does pregnancy accelerate the rate of progression of diabetic retinopathy?: An update. *Curr Diab Rep* **8:**270-273.
26. Klein BE, Moss SE, Klein R (1990). Is menarche associated with diabetic retinopathy? *Diabetes Care* **13:**1034-8.
27. Takamura Y, Tomomatsu T, Kubo E, Tsuzuki S, Akagi Yl (2008). Role of the polyol pathway in high glucoseinduced apoptosis of retinal pericytes and proliferation of endothelial cells. *Invest Ophthalmol Vis Sci* **49:**3216–3223.
28. Early Treatment Diabetic Retinopathy Study Research Group (1985). Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report No. 1. *Arch Ophthalmol* **103:**1796-1806.
29. Kim JE, Pollack JS, Miller DG, Mittra RA, Spaide RF (2008). ISIS-DME: a prospective, randomized, dose-escalation intravitreal steroid injection study for refractory diabetic macular edema. *Retina* **28:** 735–740.
30. Singh R, Abhiramurthy V, Gupta V, Gupta A, Bhansali A (2006). Effect of multifactorial intervention on diabetic macular edema. *Diabetes Care* **29:**463-4.
31. Singh R, Gupta V, Gupta A, Sachdev N, Dogra MR, Bhansali A

(2006). Multifactorial interventions before laser photocoagulation improve outcome of diabetic macular edema. *Diabetes Care* **29:**2758-9.

32. Ahmadi MA, Lim JI (2009). Update on laser treatment of diabetic macular edema. *Int Ophthal Clin* **49:**87-94.
33. Cunningham ET Jr, Adamis AP, Altaweel M, Aeillo LP, Bressler NM, D'Amico DJ, et al. (2005). A phase II randomized doublemasked trial of pegaptanib: An anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* **112:**1747-57.
34. Nguyen QD, Tatlipinar S, Shah SM, Haler JA (2006). Vascular endotherlial growth factor is a critical stimulus for diabetic macular edema. *Am J Ophthamol* **142:**961-9.
35. Chun DW, Heier JS, Topping TM, Duker JS (2006). A pilot study of multiple intravitreal injections of ranibizumab in patients with center involving clinically significant macular edema. *Ophthalmology* **113:**1706-12.
36. Haritoglou C, Kook D, Neubauer A, Wolf A (2006). Intravitreal Bevacizumab (Avastin) therapy for persistent diff use diabetic macular edema. *Retina* **26:**999-1005.
37. Strom C, Sander B, Klemp K, Aiello LP, Lund-Anderson H, Larsen M (2005). Effect of ruboxistaurin on blood-retinal barrier permeability in relation to severity of leakage in diabetic macular edema. *Invest Ophthalmol Vis Sci* **46:**3855-8.
38. Singerman LJ. Intravitreal bevasiranib in exudative age-related macular degeneration or diabetic macular edema. 25th Annual Meeting of the American Society of Retina Specialists. Indian Wells, California, December 1-5, 2007.
39. Speiser PP, Gitt elsohn AM, Patz A (1968). Studies on diabetic retinopathy, III: Influence of diabetes on intramural pericytes. *Arch Ophthalmol* **80:**332-7.
40. Sorbinil Retinopathy Trial Research Group (1990). A randomized trial of sorbinil: An aldose reductase inhibitor, in diabetic retinopathy. *Arch Ophthalmol* **108:**1234-44.