Diabetic Macular Edema (DME), a micro vascular complication of diabetes mellitus accounts for three quarter of cases of moderate visual loss due to diabetic eye disease. This entity represents a significant burden with increasing incidence and prevalence of diabetes in the Indian subcontinent, and availability of limited public health resources. In chronic poorly controlled diabetics with associated co–morbid conditions such as dyslipidemias and overt nephropathy, the edema at the macula tends to be more severe, and is characterized by the accumulation of plaques of hard exudates under the fovea, exhibiting poor response to conventional therapies and showing a tendency to becoming recalcitrant. In this situation the patient is burdened by severe visual loss, with very few management options and a poor visual prognosis. Yet DME still remains an underestimated complication of diabetes 1 primarily due to lack of awareness among the patients and primary care physicians alike.

Diabetic retinopathy is the leading cause of blindness in patients aged between 20 and 74 years in the developed world2, 3. The Wisconsin Epidemiological study (WESDR)4,5 reported that in patients with type I DM < 5 years duration, the incidence of diabetic macular edema was nil when compared to a 32 % incidence in type I DM patients whose diabetic age exceeded 20 years.

A genetic predisposition for the development of diabetic retinopathy has been found in certain studies. A polymorphism in the aldose reductase gene6,7 has been found to be associated with an increased risk of diabetic retinopathy and other micro vascular complications after controlling all independent risk factors. In contrast there are other individuals with very long duration of diabetes, and, despite mediocre diabetic control, do not develop retinopathy indicating the presence of an unknown protective factor.

Depending on the type of diabetes, the mode of treatment and the duration of disease, significant variation in the incidence and prevalence of diabetic macular edema have been reported in several epidemiological studies. **As a general rule, the lifetime risk of developing diabetic retinopathy with sight threatening complications like DME and PDR is 50 % for a patient with Type I DM and one in three for a patient with Type II DM**8.
In view of the rapidly increasing diabetic population in the developed and developing world, a dramatic increase in patients with diabetic macular edema is anticipated in the years to come. The reduced quality of life and dependency of patients with diabetic macular edema makes early screening and initiation of therapy very vital.

Pathophysiology of DME:

Vascular endothelial damage has a major contribution to the development of diabetic macular edema. The resultant breakdown of the inner blood retinal barrier causes accumulation of fluids and serum macromolecules in the intercellular space. The microvascular damage is thought to be a consequence of loss of capillary pericytes, proliferation of endothelial cells and out pouching of the vessel wall. (Fig 1)

Fig. 2. **Mild DME**: is characterized by retinal thickening and hard exudates in the posterior pole, but distant from the centre of the fovea.

Fig. 3. **Moderate DME**: is characterized by retinal thickening and hard exudates in the posterior pole, approaching the centre of macula, but not involving the fovea.

Fig. 4. **Severe DME**: is characterized by hard exudates involving the centre of the fovea.

Grading of DME

Diabetic macular edema is defined as retinal thickening due to fluid leakage and pooling in the macular area. The International DME severity scale \(^{16}\) grades DME based on its severity into mild, moderate and severe. (Fig: 2, 3, 4)

Clinically significant diabetic macular edema:
The ETDRS \(^9\) was one of the first large clinical trials sponsored by the National Eye Institute and this study coined the term ‘clinically significant macular edema (CSME)’ for edema that threatens or involves the centre of the fovea. Thus CSME includes

1. Thickening of retina at or with in 500 μm of the centre of the macula. (Fig 5).
2. Hard exudates at or with in 500 μm of the centre of macula, if associated with thickening of the retina.
3. A zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula.

Types of Diabetic Macular Edema

Diabetic Macular Edema can be clinically divided into **focal, diffuse, mixed, cystoid and ischemic.**

FOCAL DIABETIC MACULAR EDEMA

In focal diabetic macular edema there are localized areas of retinal thickening caused by focal leakage from retinal capillaries or micro aneurysms. These areas are frequently demarcated by partial or complete ring of hard exudates called circinate rings. (Fig 6)
**Diffuse Diabetic Macular Edema:**

In diffuse diabetic macular edema there is more widespread thickening of the macula secondary to generalized abnormal permeability of the retinal capillaries. This generalized leakage is thought to be the result of compensatory dilation of parts of the perifoveal capillary net in response to occlusion of neighboring parts of the capillary bed. (Fig 7)

Risk factor for progression of diffuse macular oedema are increasing micro aneurysm count\(^1\) adult onset diabetes, hypertension, cardiovascular disease, vitreo macular adhesion and advanced retinopathy\(^1\). In clinical practice however a variety of mixed forms may be encountered.

**Cystoid Macular Edema:** is characterized by the presence of cystoid spaces filled with an ophthalmoscopically clear fluid. This is not pathognomonic of diabetic macular edema but may be associated with various other conditions. The presence of an intact attached and thickened posterior hyaloid plays a role in its pathogenesis\(^2\). The presence or absence of this entity does not influence either the prognosis or management. (Fig 8)

**Ischemic Macular Edema:** The nonperfused or the ischemic variant of diabetic macular edema is characterized by very poor central visual acuity, grossly edematous macula, and fluorescein angiographic evidence of enlarged foveal avascular zone (FAZ) and occlusion in the capillary bed of the perifoveal network. Only fluorescein angiography can document the degree of ischemia and the location of the capillary non perfusion (CNP) areas. (Fig 9)

**Diagnosis and screening**

Diabetic macular edema in its early stages does not cause loss of visual function. The goal of therapy is rarely improvement of vision, on the contrary, in most cases, it is preservation of vision and avoidance of further damage. Hence it is necessary to detect retinopathy before visual loss and irreversible changes set in.

There is controversy regarding the modality of screening to be employed, to screen regularly the millions of diabetic patients. Though dilated fundus examination is highly sensitive and specific; it imposes a huge work load and requires a high density of qualified and trained health care providers. However a binocular stereoscopic slit lamp biomicroscopy still remains the most important diagnostic tool. In a remote area this method of detection may not be feasible. Fluorescein angiography is helpful in detecting leaking points and ischemia prior to treatment but being an invasive intervention it is not appropriate for routine screening.

Optical coherence tomography allows a non invasive quantitative and examiner-independent evaluation of macular edema as well as assessment of the presence or absence of vitreo macular traction. However being an expensive modality it cannot be used for screening.

Developments of screening technique using telemedicine in remote areas have generated a lot of interest in digital fundus photography with automated grading of diabetic changes. \(\text{e.g.: micro aneurysm counting}\)\(^1,\)\(^4\), \(^15\)

Although screening and early detection is vital, it does not replace a formal eye examination with patient counseling.

**Imaging in the Quantification of DME**

A slit lamp stereoscopic examination is all that is necessary in the routine diagnosis of diabetic macular edema. However further imaging studies are necessary for the following reasons.

1. To grade the severity of the macular edema.
2. To assess the presence of macular edema and the integrity of the perifoveal capillary network.
3. As a guide to decide on the modality of treatment for a specific given patient.
4. To assess the efficacy of treatment modality employed and to decide on retreatment.
5. To follow up patients with non significant DME.
6. To screen patients for diabetic retinopathy (rarely done)

The imaging modalities used to quantify diabetic macular edema includes 1) Colour fundus photographs: 30° and 50° stereo photographs 2) Fluorescein fundus
angiography (FFA) 3) Optical Coherence Tomography (OCT) 4) RTA 5) SLO and HRT.

Fluorescein Fundus Angiographic Abnormalities in Diabetic Retinopathy: FFA has the advantage of being the only imaging modality that can assess the integrity of the perifoveal capillary net, localize areas of capillary non perfusion as well as areas of leakage of the dye. The pattern of dye leakage in a fluorescein angiogram helps to differentiate between focal, diffuse, mixed, ischemic, and cystoid varieties of diabetic macular edema. (Fig 10 a, b, c)

The earliest fluorescein angiographic changes in diabetic retinopathy in the presence of capillary microaneurysms (Fig 11). Other angiographic changes include the presence of leakage at the macula; development of capillary non perfusion areas and widening of FAZ, intraretinal micro vascular anomalies (Fig.12); neovascular fronds on the disc (NVD) and else where in the retina (NVE).

Fluorescein fundus angiography also helps to identify presence of associated lesions at the macula such as idiopathic parafoveal telangiectasia, macular drusen etc (Fig 13)

The disadvantages of relying on fluorescein angiographic findings alone are its inability to quantify the severity of diabetic macular edema and also the amount of leakage does not correlate with the degree of retinal thickening. The presence of serious side effects and its interventional nature also prevents FFA from being accepted as a ‘stand alone’ diagnostic and screening tool.

Role of Optical Coherence (OCT) In Diabetic Macular Edema

Optical Coherence Tomography is a fast and noninvasive tool for examining the retina in cross sectional images that correlates reasonably well with the retinal histology\(^\text{17}\). OCT is a sensitive diagnostic test that helps in the early detection of diabetic macular edema. Being non invasive its acceptance as a follow up imaging modality to monitor the course of DME and response to therapy is high. OCT has the added advantage of being able to reveal the presence of cystoid macular edema, sub foveal serous retinal detachment, presence of vitreomacular traction or an epiretinal membrane, which cannot be detected in a fluorescein angiogram. Moreover the macular thickness map gives us as very accurate idea of the central retinal thickness and can quantify the degree of improvement or worsening following therapy.

Several different patterns of structural changes have been demonstrated with in the retina in diabetic macular edema\(^\text{18,19}\). These include 1. Sponge like retinal thickening (Fig 14 ) 2. Cystoid macular edema (Fig 14 b) 3. Sub foveal sensory retinal detachment (Fig 14 c) 4. Taut attached posterior hyaloid phase (Fig 14 d) 5. Presence of vitreomacular traction (Fig 14 e): and screen effect produced by a plaque of hard exudates (Fig. 14 f).

Thus OCT separates cases of diabetic macular edema with vitreo retinal interface abnormalities\(^\text{19}\) (such as vitreomacular traction, coincident epiretinal membrane and taut internal limiting membrane) and helps us to understand why these eyes respond poorly to pharmacological and laser therapies. It helps to selectively identify cases of diabetic macular edema, which needs surgical intervention.

Based on the central retinal thickness in the optical coherence tomogram, macular edema is classified\(^\text{19,20}\) into mild, moderate and severe.

\[ \begin{align*}
\leq 200 \mu m: & \text{ Normal} \\
201 \mu m- 300 \mu m: & \text{ Mild thickening} \\
301 \mu m- 400 \mu m: & \text{ Moderate thickening} \\
\geq 400 \mu m: & \text{ Severe thickening}
\end{align*} \]

Treatment Options

Treatment of diabetic macular edema combines the optimization of systemic risk factors with systemic and local pharmacological treatment, as well as laser intervention and surgical approaches. Ophthalmologists may play a key role in patient motivation, and effective co operation with the general practitioners, primary care physicians, and endocrinologists is essential.

**Systemic Treatment:** - Effective treatment for diabetic macular edema is not possible unless all the components of the metabolic syndrome are kept under rigid control (Fig 15)
Systemic treatment for diabetic macular edema includes:

1. Glycemic control
2. Blood pressure control
3. Reducing levels of blood lipids
4. Treatment of renal dysfunction
5. Systemic pharmacotherapy
   - PKC-β inhibitors
   - Aldose reductase and AGE Inhibitors
   - Antioxidants

Glycemic Control:

Tight blood glucose control is essential for prevention of end organ damage and complications including diabetic retinopathy and macular edema. The WESDR showed a strong relationship between baseline glycosylated hemoglobin (Hb A₁C) and the incidence of macular edema over a ten-year period. The diabetic control and complications trial (DCCT) demonstrated a 26% reduction in the risk of developing macular edema in the intensive insulin treatment group as compared with the conventional treatment group in patients with type I diabetes. Although tight glycemic control is strongly recommended for all patients with diabetes, there is no specific HbA₁C value above which the risk of developing diabetic retinopathy increases. Since very rigid control in chronic diabetics carries the risk of hypoglycemic complications, an HbA₁C level of 7.0% is the highest level recommended by the American Diabetes Association guidelines. In addition to being a risk factor for the development of diabetic macular edema, elevated Hb A₁C has been associated with a poor response to laser therapy and bilateral disease. Thus tight blood glucose control is cost effective as it substantially reduces the cost of managing complications.

Blood pressure control

- WESDR results have conclusively shown that in patients with type 1 DM; and a diastolic blood pressure within the forth quartile range had a 3.3 fold increased risk of developing macular edema compared to patients with diastolic BP within the first quartile range.
- UKPDS (The UK Prospective Diabetic Study) reported a 47% reduction in the loss of three or more lines of visual acuity associated with a tight blood pressure control in patients with Type II diabetes.
- The ABCD study (The Appropriate Blood Pressure Control In Diabetes) failed to demonstrate any significant effect of intensified BP control in patients with Type II DM. This could be attributed to the lower blood pressure at baseline and poorer glycemic control in the study population of ABCD study.

Reducing Levels of blood lipids.

- In ETDRS there was a positive correlation between elevated lipid levels and an increased risk of developing hard exudates and decreased visual acuity.
- The DCCT show a predictive value of total cholesterol: HDL cholesterol ratio and LDL for development of clinically significant diabetic macular edema.
- However there is no concrete evidence on the efficacy of lipid lowering agents in preventing the accumulation of hard exudates at the macula.

TREATMENT OF RENAL DYSFUNCTION AND ANAEMIA have resulted in improvement in the diabetics retinopathy status although there are no definite controlled trials supporting these anecdotal observations.
SYSTEMIC PHARMACOTHERAPY: includes the use of
1. Oral PKC-β Inhibitors (Ruboxistaurine Mesylate)
2. Aldose reductase inhibitors
3. Advanced Glycation End product (AGE) inhibitors
4. Antioxidants.

Oral PKC - β Inhibitor :-
Proteinkinase C includes a group of iso enzymes involved in intracellular signal transduction. This isoenzyme gets activated in response to a number of stimuli, an important one being hyperglycemia. Activation of PKC - β results in endothelial cell proliferation as well as an increased vascular permeability both of which are responsible for the neovascular as well as macular complications of diabetic retinopathy. In addition PKC - β is involved in the up regulation of vascular endothelial growth factor (VEGF). Administration of PKC β inhibitor has a definite effect on suppressing the VEGF induced leakage from the retinal blood vessels. The PKC- DRS2 study results show that treatment with Ruboxistaurin was associated with
1. Reduced need for initial focal photocoagulation (26 % reduction)
2. Reduced visual loss in eyes that required focal photocoagulation (40 % reduction of visual loss)
3. Reduced progression of diabetic macular edema to within 100 μm of the centre of fovea (26 % reduction)
4. Increased chance of moderate visual gain
However this study did not achieve its primary end point. Further trials are underway to study the efficacy of this drug in preventing visual loss in diabetic patients.

Aldose Reductase and AGE Inhibitors
The presence of hyperglycemia causes increase in the activity of the polyol pathway resulting in an accumulation of sorbitol. This build - up of intracellular sorbitol results in cellular damage 30. Clinical trials using aldose reductase inhibitors (to inhibit the endothelial aldose reductase activity) claim to have reduced the number of non perfused capillaries, fluorescein leakage, and micro aneurysm count. But there has been no documented effect on the progression of diabetic retinopathy 31.

Increased formation of advanced glycosylation end products (AGE) in diabetes have been proposed as another mechanism causing endothelial cell damage. In animal models, the AGE inhibitor, amino guanidine, effectively inhibited the development of diabetic retinopathy 33. Clinical trials with a novel AGE inhibitor 33 has been successful in animal models but its efficacy in treating people with diabetes has not been proved.

ANTIOXIDANTS
Hyperglycemia is followed by increased production of free radicals (Reactive Oxygen species) by various mechanisms. These radicals play a key role in the development of micro vascular complications of diabetes34. Hence reduction of free radicals should have a beneficial effect on diabetic retinopathy.

Calcium dobesilate 35 is a potent antioxidant registered for treatment of diabetic retinopathy in more than 20 countries. It has been shown to have a beneficial effect on vascular permeability and erythrocyte membrane properties in vitro and in animal models 36, 37,38. Its beneficial effects clinically have not yet been conclusively proved.

Laser Photocoagulation
Laser PHC has been the sole modality of therapy for diabetic macular edema and even now despite the availability of vitreous surgery and intravitreal pharmacotherapy; it still remains the gold standard of treatment.

The Early Treatment Diabetic Retinopathy Study 9, a multicentered randomized clinical trial (1980- 1989) sponsored by the National Eye Institute clearly demonstrated the effect of laser treatment in patients with diabetic macular edema, and also defined the term ‘clinically significant macular edema’ (CSME). The ETDRS showed that the risk of moderate visual loss (3 or more lines on a LOGMAR chart) was reduced by 50 % in eyes treated with immediate laser photocoagulation, compared to eyes in the deferral group (15 % Vs 32 %) (Fig 16 ).
Although this study was completed almost 20 years ago, the principles of laser treatment for diabetic retinopathy and macular edema is still based on its guidelines.

**Focal Laser Photocoagulation:**

The goal of focal laser photocoagulation is to seal focal leaking micro aneurysm. The preferred end point is to obtain a darkening or whitening of the micro aneurysm. Spot size 50-200 μm/0.1s/100-200 mw is the recommended laser parameters (Fig.17). However in treating micro aneurysms close to the fovea, a spot size of 50 μm / 0.055 s / 100 mw is used. Clumps of micro aneurysms close together can be treated by a larger spot size if away from fovea. The modified ETDRS focal photocoagulation protocol recommends direct treatment of micro aneurysms and grid photocoagulation to other areas of thickening.

**GRID LASER PHOTOCOAGULATION** is applied to areas of thickened retina showing diffuse fluorescein leakage and / or capillary dropout with any associated focal leak treated as outlined above. Retinal leakage or capillary dropout identified by fluorescein fundus angiography are treated with 100-200 μm burns of light intensity with constant attention to energy levels, as the uptake in these areas can be variable. At least one burn width is spaced between burns. Areas of intense leakage are treated with grid spots one burn width apart, while areas of less intense leakage are treated by more widely spaced burns. The grid is placed within 500 μm of the disc margin, but can be placed on the papillo macular bundle. It can extend in all directions up to 2 DD from the centre of fovea, or up to the border of the PRP treatment (Fig.18).

**Micropulsed, Sub Threshold Selective Laser Therapy:**

Histological studies have shown that there may be a full thickness retinal reaction even to barely visible laser burns. In clinical pilot studies sub threshold laser coagulation (Using a green Nd: YLF micro pulsed laser) was effective in eyes with diabetic macular edema, while minimizing chorioretinal damage.

Laser photocoagulation of the macula is inherently destructive and creates small areas of irreversible damage to the retinal tissue. Furthermore, enlargement of the laser scars with progression into the central foveal area and subsequent loss of vision has been reported.

Currently much lighter intensities are used in order to obtain a barely discernible reaction of the RPE. For very central leaks observation combined with improved systemic disease control are preferred and treatment at the margin of the FAZ is avoided. If there are no appropriate targets for foveal laser photocoagulation demonstrated by FFA, laser PHC is usually deferred and other modalities of therapy suggested to the patient.

**Intravitreal Steroids:** - The role of steroids is mediated through 1) Suppression of VEGF 2) Stabilizing the leakage from retinal vessels 3) Suppression of the release of endothelial cell activators and 4) Possibly its anti-inflammatory action.

Initially uncontrolled interventional case series reported an unprecedented efficacy of intravitreal steroids (usually triamcinolone acetonide) in reducing diabetic macular edema accompanied by significant improvement in visual acuity. These uncontrolled series were followed by randomized placebo controlled trials demonstrating the efficacy of IVTA compared with standards care on both short and long term.

Several studies in eyes with persistent DME despite focal and / or grid laser photocoagulation have demonstrated the efficacy of IVTA over laser.

Although most studies have shown a beneficial effect the optional dosage of IVTA is still somewhat confusing. Audren F et al conducted a randomized prospective trial comparing the efficacy of 2 mg vs. 4 mg of Triamcinolone acetonide in the management of diffuse diabetic macular edema. Their results showed that there was no dose dependent difference in the response to intervention. However Lam DS et al and Spandau et al demonstrated dose dependency in the response to intravitreal injection of triamcinolone acetonide.

The beneficial effect of an intravitreal injection of triamcinolone acetonide in most cases lasts for 6 months to 9 months and repeated injection may not be as efficacious as the initial treatment.

The high incidence of steroid related adverse effects such as (1) necessity for cataract extraction in 54 % of
phakic treated eyes (2) steroid related elevation of IOP in 44 % of treated eyes necessitates the use of caution.

In order to avoid the adverse effect associated with intravitreal therapy, particularly infectious endophthalmitis, the use of periocular steroids in the management of diabetic macular edema has been studied 58, 59. The results of these trials have been contradictory to each other showing either a beneficial effect or no appreciable effect of the intervention on DME.

**Intravitreal Anti VEGF Antibodies: Bevacizumab and Ranizumab**

Vascular endothelial growth factor (VEFG) has been shown to be an endothelial cell- specific mitogen and an angiogenic inducer in a variety of in vitro and vivo models. VEGF; also known as vascular permeability factor; has been demonstrated to increase retinal vessel permeability by increasing the phos-phorylation of tight junction proteins. All variants of VEGF (particularly VEGF-A) have been implicated in the occurrence of increased vascular permeability by affecting endothelial tight-junction proteins in ocular vascular diseases such as diabetic macular edema (DME). VEGF-Levels are considerably higher in DME patients with extensive leakage in the macular region than in the patients with minimal leakage. Recent work has found elevated levels of VEGF in ocular fluids of patients with proliferative diabetic retinopathy (PDR). These studies also found that the growth of new vessels from the retina or optic nerve was thought to occur as a result of VEGF release into the vitreous cavity as a response to ischemia.

**Avastin in the management of DME**

Studies have demonstrated the usefulness of an intravitreal injection of Bevacizumab with promising effects in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability and fibro vascular proliferation in retinal neovascularisation secondary to PDR, rubeosis iridis, retinopathy of prematurity, and choroidal neovascularization secondary to AMD, and in the treatment of DME.

The use of Anti – VEGF drug is becoming increasingly more prevalent; however some unresolved issues such as the ideal regimen, duration of treatment, potential of combination treatments, and safety concerns with long term VEGF inhibition deserve further investigations.

Investigators continue to report their experience with intravitreal injections of Bevacizumab, a humanized monoclonal Ig G antibody directed against all five VEGF isoforms, in the setting of primary therapy. In a study of 51 patients, Haritoglou et al. observed that at 6 weeks after a single Bevacizumab injection, patients with DME resistant to other therapies had increased visual acuity as well as decreased central retinal thickness by OCT relative to pre-injection baseline, though the effect on visual acuity was not sustained at 12 weeks 60. The Pan – American Collaborative Retina Study (PACORES) Group studied intravitreal Bevacizumab as a primary treatment for DME in 78 eyes of 64 patients and found, at six months, over 96 % of eyes had either stable or improved visual acuity or reduction in the mean central retinal thickness by OCT. A phase II DRCR net study of 109 patients compared two does of Bevacizumab to focal laser photocoagulation and demonstrated its efficacy in decreasing DME in some eyes. To date, no phase III trials have been reported that demonstrate a clear benefit for Bevacizumab in the treatment of DME.

A report by the Pan - American Collaborative Retina study Group on 101 consecutive eyes with diffuse diabetic macular edema (DDME) treated with intravitreal Bevacizumab, resulted in both anatomic and functional improvement62. Interestingly, the reduction of retinal thickness and improvement of BVCA were detected within the first 4 weeks after the injection in most of the patients. In addition, both doses (1.25 mg and 2.5 mg) were associated with improvement of BVCA and a greater reduction in central macular thickness, and no difference in between were found. Ocular tolerance of the 2 different doses of IVB was demonstrated, and no serious systemic adverse events were noticed during the study.

There are several studies in the literature on the intravitreal administration of antibodies against VEGF for DDME. However, none of them deal with anti-VEGF as a primary treatment. Haritoglou et al reported that intravitreal ranibizumab has the potential to maintain or improve BVCA and reduce retinal thickness in patients with DDME not responding to previous treatments such as photocoagulation, intravitreal
injection of triamcinolone, or vitrectomy. Their follow-up period was too short (6 weeks) to provide specific treatment recommendations. Kumar and Sinha\textsuperscript{63} reported results of 20 eyes with DDME treated with IVB dose of 1.25 mg that had not responded to previous photocoagulation. Their follow-up period was 6 months. They concluded that IVB resulted in a significant decrease in macular thickness and improvement in visual acuity at 3 months, but the effect was somewhat blunted, though still statistically significant at the end of 6 months. The current study\textsuperscript{62} compares favorably with these reports, and confirms their findings with longer follow up and a larger number of patients. Further more, at the 6 month follow-up time point they also noticed a small worsening of vision as described by Kumar and Sinha. When analysis of data comparing eyes that had 1 or 2 injections against those eyes that had 3 or more injections was performed, there was a significant drop in BCVA at 6 months in the “1 or 2 injections” group, and not in the “3 or more injections” group. This suggests the need for at least 3 injections a year to maintain the BCVA results. 64 eyes (63.4 \%) needed at least a second injection at a mean of 15.7 ± 11.9 weeks (range: 4 to 64 weeks).

The results of this retrospective study demonstrated the efficacy of 1.25 mg or 2.5 mg of IVB as primary treatment of DDDME, as 49.5 \% of eyes showed anatomical and functional improvement. In addition, the results suggest a reduced risk of visual acuity loss in eyes with DDME treated with intravitreal bevacizumab (IVB) (82.2 \% of eyes). The anatomical and visual benefit of the intravitreal Bevacizumab appears and reaches its maximum value during the first month maintains itself over 12 months. Nevertheless, statically significant differences between the 2 doses of Bevacizumab evaluated could not be demonstrated.

**Ranibizumab in DME (READ Trial)**

While ranibizumab, a humanized monoclonal antibody fragment directed against all VEGF isoforms, is currently in clinical trials for DME, its off label use in DME patients is limited most likely as a result of its increased cost and less wide spread availability world wide, as compared to Bevacizumab. Two pilot studies of ten patients each suggested that it was well tolerated and may have some efficacy in promoting improvement in visual acuity and reduction in central retinal thickness by OCT.

A phase 1 study (the READ-1 Study, Ranibizumab for Edema of the macula in Diabetes, sponsored by the Juvenile Diabetes Research Foundation) of 20 patients with DME treated with intravitreal Ranibizumab (IVB). Repeated intravitreous injections 0.5 mg of ranibizumab, showed evidence of biological activity of ranibizumab in DME as well as safety and tolerability (Nguyen, et al. 2006)\textsuperscript{64}. In the Phase 1 study, patients were given intravitreal ranibizumab at baseline and at months 1, 2, 4, and 6. Results showed that at month 7, one month after the final administration of ranibizumab and the primary endpoint of the study, the median reduction of the excess foveal thickness was 97 \%, and there was a median improvement of 10 letters.

There have been no adverse events that were believed to be related to the study drug; in particular, intraocular inflammation was not observed.

The READ-2 Study is a Phase 2 randomized, multicenter clinical trial sponsored by the Juvenile Diabetes Research Foundation. The study enrolled 126 patients from 14 clinical centers throughout the United States.

Proportion of subjects who gain 15 or more letters, or achieve a final vision of 50 letters (20/25) or better if baseline VA was 40 letters (20/40) or better, at 6 months was the primary endpoint.

Patients were eligible if they had an ETDRS Visual acuity of 20/40 or worse, but better than or equal to 20/320 due to foveal thickening from macular edema secondary to diabetes (type 1 or 2) and a baseline foveal thickness of 250 \(\mu\)m on OCT.

Each study subject in the trial was randomized 1:1:1:1 to 1 of 3 treatment groups.

- **Group 1** (ranibizumab only)
- **Group 2** (Laser)
- **Group 3** (ranibizumab and laser)

The patients were followed every 12 weeks until 24 months (secondary time endpoint). At any study visit, if there is an increase of a specified amount of retinal thickness on OCT that meets re-treatment criteria, the patients will have the opportunity to receive an additional injection of ranibizumab plus laser 7 days later.
The re-treatment criteria for patients in all 3 randomized groups were an absolute retinal thickness in OCT central subfield of <250 μm (at time of study visit). Six months outcomes suggest greater improvement in visual acuity for patients receiving intravitreal Ranibizumab as compared to those receiving laser or combination therapy.

**Combination Therapy**

As diverse mechanism and patterns of DME are recognized, clinicians are using multi-model therapies to approach DME. In theory, targeting various pathologic mechanisms of DME with combination therapies may have a more lasting effect on reversing and maintaining a clinical benefit to the patients. Commonly focal laser photocoagulation is being combined primarily with Ocular Steroid therapy (either IVTA (Intravitreal injection of Triamicinolone acetonide) or PSTTA (Posterior subtenons injection of Triamicinolone acetonide) or anti VEGF agents. This strategy seeks to take advantage of the more immediate effects of pharmacologic agents while employing laser therapy for long term stabilization. Anti VEGF agents have been used to salvage eyes refractory to steroid therapy, in eyes experiencing steroid related side effects, and more recently in combination with IVTA therapy with positive results. Pharmacological agents are also being used at the time of vitrectomy surgery help to prevent recurrent DME.

**Surgical Management of Diabetic Macular Edema**

Surgical options in the treatment of recalcitrant diabetic macular edema includes pars plana vitrectomy combined with peeling of epiretinal membranes and or internal limiting membranes and removal of subretinal hard exudates.

The vitreous gel is thought potentially to play a role in the development of DME through mechanical factors and / or physiologic mechanisms that lead to increased retinal vascular permeability. Vitrectomy has been used in the management of diabetic macular edema (DME) for many years. In many cases, this surgical procedure is performed because of macular traction and abnormality of the posterior hyaloid.

In some cases, the procedure has been performed as a “last-resort” measure in the judgment of an ophthalmologist when the eyes have been non responsive to macular photocoagulation and other modalities. Despite the fact that thousands of eyes are estimated to have had vitrectomy for DME, available data, to judge the merits and risks of surgical procedure for DME is limited. The literature consists mainly of retrospective case series.

There are at least 2 avenues of investigation that support the theoretical value of vitrectomy for the treatment of DME, based on (1) vitrectomy to relieve biomechanical traction on the macula and (2) vitrectomy to improve oxygenation of the macula leading to decreased permeability with subsequent resolution or decrease in DME.

Vitrectomy to relieve biomechanical traction on the macula has been reported widely.

The DRCR net Study evaluating vitrectomy for DME (Protocol D, available online at www.drcr.net) is designed as a prospective cohort study in patients with DME on clinical examination and a best corrected vision of 20/800 or better.

**Study Objectives were:**

1. To provide information on the following outcomes in eyes with DME that undergo vitrectomy: visual acuity (VA), retinal thickening, resolution of traction (if present), surgical complications.
2. To identify sub groups in which there appears to be a benefit of vitrectomy and sub groups in which vitrectomy does not appear to be beneficial.
3. To obtain data that can be used to plan a randomized trial.

The 6 months results of this clinical trial (presented at the AAO subspeciality meeting 2008 at Atlanta) showed favorable results with vitrectomy.

Triamcinolone assisted pars plana vitrectomy is preferred by many surgeons as the TA helps delineate the posterior cortical vitreous, epiretinal membrane and the internal limiting membrane. The half life of Triamcinolone acetonide in the vitreous cavity in a vitrectomised eye is only 1-6 days. The small amount of TA crystals sequestered in the vitreous cavity is not
Fig. 5: ETDRS definition of clinically significant diabetic macular edema. (Adapted from ETDRS report, Ophthalmology 1987)

Fig. 6: Focal DME characterized by focal areas of retinal thickening and a partial or complete ring of hard exudates.

Fig. 7: Diffuse DME demonstrating generalized abnormal permeability of retinal capillaries

Fig. 8: (a) Flower petalloid appearance on fluorescein fundus angiography due to pooling of dye. (b) OCT characterized by cystoid space in an edematous retina filled with clear fluid.

Fig. 9: Ischemic Maculopathy is characterized by gross macular edema, fluorescein angiographic appearance of enlarged foveal avascular zone (FAZ) and loss of integrity of the perifoveal capillary net.

Fig. 10: a, b and c: (a) focal diabetic macular edema, (b): diffuse DME with neovascularization elsewhere (NVE) (c): ischemic maculopathy

significant enough to cause a postoperative intraocular pressure spike, but may be just enough to prevent postoperative intraocular inflammation.

The concept of denuding the inner retinal surface of the internal limiting membrane promotes migration of cells, egress of extra cellular fluid and blood out of the
Fig. 13. Idiopathic parafoveal telangiectasia (IPFT) can co exist with diabetic macular edema.

The retina and towards the vitreous cavity. Reduction in retinal thickening and improvement in oxygenation should theoretically improve the visual acuity.\textsuperscript{76,77}

The use of Indocyanine green (ICG) to assist internal limiting membrane peeling has been associated with reports of retinal and optic nerve toxicity. The adverse effects of ICG\textsuperscript{78} assisted ILM peeling has been reported in 46.7\% of subjects who developed slowly progressive onset of optic atrophy with in 6 months of undergoing surgery, associated with irreversible peripheral visual field defects predominantly in the nasal field. Other reports on vitrectomy with ILM peeling for diabetic macular edema or macular hole surgery does not show any intraoperative or postoperative complication attributed to the use of ICG or any clinical or angiographic evidence of ICG toxicity. Other dyes have been used for internal limiting membrane peeling including Trypan blue and Brillinat Blue G.

The role of vitrectomy with ILM peeling in the management of eyes with diffuse diabetic macular edema without a taut posterior hyaloid, refractory to standard laser treatment has been extensively studied. Most of these studies (TABLE: 1) have shown that the results of PPV with ILM peeling lead to resolution of DME, but was not always associated with visual improvement. In diabetic eyes, CME and subfoveal serous retinal detachment were poor prognostic indicators for visual recovery.

Various other groups of workers have conclusively shown that PPV with ILM peeling leads to expedited resolution of diffuse diabetic macular edema and visual improvement without subsequent epiretinal membrane formation. Quantitative assessment of OCT images at the end of follow up revealed that retinal thickness in the macula appeared nearly normal with or without reappearance of foveal pit in 73.3 \%. The effects of
### AUTHORS/ YEAR | NO. OF EYES | MACULAR THICKNESS | VA | RESULTS
---|---|---|---|---
GANDORFER 2000 | 12 | Resolution 4-12 weeks | 2 line all eyes | Favourable
Ando F, 2004 | 15 | Resolution to Normal (20 %) Improved (26.7%) | OA in 46.7 % | 
Shah, Patel & Tomas etal 2006 | 33 | Resolution | Improved only in Pts with VMT | Unfavourable
Behadir 2005 | 58 | Similar in both groups | Similar in both groups | No added benefits
Parys Vanginderdeuren et al 2005 | 26 | Resolution | Improved | Good
Gaurav Shah 2005 | 26 | Good resolution | 2 line improvement | Good

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**Fig. 14.** (a) Spongy retinal edema (b) Cystoid Edema (c) Subfoveal serous retinal detachment (d) Taut attached posterior hylaoid (e): Vitreo macular traction (f): Screen effect produced by plaque of hard exudates.
resolution of macular edema, reduction in retinal thickness and improved visual function were longer lasting than following IVTA injection. The visual improvement following PPV with ILM peel was gradual and occurred within 6 months to one year following the surgery.

**Synopsis:**

Diabetic Macular Edema is one of the major causes for moderate visual loss in a diabetic. With increasing incidence and prevalence of diabetes and limited public health resources, diabetic macular edema is becoming a major public health concern.

**Current Clinical Practice/Recommendations for DME**

- A detailed history on the duration of diabetes, adequacy of control, presence of other complications, current medications, glycaemic and blood pressure control, history of prior eye surgery, prior laser treatment and speed and duration of visual loss is taken.

- Ophthalmic evaluation includes
  1. Best Corrected Visual Acuity
  2. Tonometry
  3. Slitlamp Biomicroscopic examination of the macula
  4. Assessment of Lens Changes
  5. Detailed fundus evaluation after adequate mydriasis
  6. Stereofundus photography
  7. Baseline fluorescein fundus angiography
  8. Optical Coherence Tomography

- Based on clinical evaluation, angiographic and tomographic assessment the maculopathy can be divided into
  - Focal
  - Diffuse
  - Ischemic
  - Cystoid
  - Mixed
  - VMT

- Macular edema with subfoveal serous RD
Special attention should be paid to the vitreoretinal interface (for presence of traction, PVD, thickened taut post hyaloid, epiretinal membranes)

Depending on these findings one of the following treatment options is offered to the patient.

1. In patients with poor and improvable systemic control or diabetic renal disease with stable visual acuity or a slow decrease in vision, initiation of better systemic control (blood sugar, blood pressure, and hemodialysis, anemia) should be the first step. Specific Ophthalmologic treatment may be deferred until systemic factors are optimized.

2. For patients with **Focal Diabetic Macular Edema without significant ischemia** focal laser is still the treatment of choice. Compared with the ETDRS guidelines, use of lighter burns of longer duration and to perform more than one session of treatment in severe cases is recommended.

3. For patients with **diffuse diabetic macular edema** modified grid laser photocoagulation sparing the fovea can be performed if the OCT shows a central retinal thickness $\leq 300 \, \mu m$ and there is no evidence of ischemia.

**Micro pulsed Sub threshold Selective Laser Therapy:** Using a given Nd:YLF micro pulsed laser has been shown to be effective in DME, while minimizing chorioretinal damage.

4. **Intravitreal or Peribulbar steroids** are recommended in cases where the laser treatment has not been effective or seems unlikely to improve. If the eye is phakic the risk of steroid induced cataract has to be discussed. Pre existing glaucoma or a family history of glaucoma should be taken into account.

5. Intraocular pressure has to be followed closely. Eyes with gross **diffuse macular edema and subfoveal serous retinal detachment** respond best to intravitreal injections.

6. After IVTA the situation should be re-evaluated and **laser photocoagulation** applied if appropriate.

7. **Vitrectomy combined with peeling of epiretinal membranes and internal limiting membranes** may be considered for eyes with pathology in the vitreoretinal interface. This procedure may be preceded by or combined with intravitreal steroids.

8. For all these options the other features of diabetic retinopathy should be taken into account and therapeutic approaches can be combined (**focal laser followed by PRP; IVTA followed by PRP; IVB followed by PRP, vitrectomy combined with endolaser photocoagulation etc.**)

9. In cases of uncontrollable adverse effects of steroids after IVTA, or persistent or relapsing edema with gross visual deterioration, treatment with intravitreal Anti VEGF agents is considered.

10. The efficacy of these therapeutic measures should be regularly monitored and strategies varied depending of visual acuity, clinical findings and onset of complications.

11. The risk of diabetic macular edema worsening after uneventful cataract surgery is a definite possibility. Risks and potential benefits should be
weighed against each other based on the clinical situation. Postoperative monitoring and early initiation of treatment can effectively check this risk of progression of diabetic macular oedema after cataract surgery.

11. Ophthalmologists play an important part in patient motivation. A team approach with the internist, endocrinologist, and nephrologists is absolutely necessary.

12. Systemic Pharmacotherapy: **Oral PKC β inhibitor Ruboxistaurine** has been found in experimental studies to reduce the risk of vision loss (40% reduction), need for laser photocoagulation (26% reduction) and progression of macular edema (26% reduction) compared with the placebo.

13. Other systemic pharmacotherapeutic agents of use in treatment of diabetic macular edema are aldose reductase and AGE inhibitors and antioxidants.

**Reference**


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