Diabetic macular edema (DME) is one of the major causes of vision loss in patients with diabetic retinopathy. It is defined as retinal thickening in the posterior pole essentially resulting from increased permeability of retinal vasculature leading to the disruption of the blood retinal barrier and other alterations in the retinal micro-environments.

Though chronic hyperglycemia is the primary factor leading to the development of diabetic retinopathy, the mechanisms by which elevated blood sugar levels lead to the development of DME and the histopathologically visible changes are still not clear.

DME may result from leakage of micro aneurysms or it may be due to diffuse leakage of hyper permeable capillaries. It may or may not be characterised by intraretinal cyst formation and also sub retinal fluid in the settings of severe cystic thickening involving the fovea. To characterize the severity of macular edema and for treatment guidelines, the term clinically significant macular edema (CSME) is used. Macular edema is clinically significant if one of the following conditions is present: retinal thickening at or within 500 um of the center of the macula; and/or hard exudates at or within 500 um of the center of the macula if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disk area in size, at least part of which is within 1 disk diameter of the macular center.

Pathogenesis of diabetic macular edema

Biomechanical mechanisms in pathogenesis of diabetic macular edema

1. The aldose reductase pathway

Aldose reductase uses the reduced form of nicotinamide adenine dinucleotide phosphate as a cofactor to reduce many aldose sugars into their respective sugar alcohol. Glucose is reduced to sorbitol, which is then oxidised to fructose by sorbitol dehydrogenase. In normoglycemic conditions, the aldose reductase pathway is non-operative as glucose is a poor substrate for aldose reductase because of its high binding constant. Although, in the settings of hyperglycemia the aldose reductase pathways are activated which further lead to osmotic stress due to accumulation of sorbitol. Increase in the utilisation of aldose reductase in the hyperglycemic state of diabetes will result in a decline of intracellular NADPH that alters the cellular redox balance. These lead to oxidative stress and result in cellular damage.

2. Advanced glycation protein endproduct theory

Nonenzymatic glycation and cross linking of proteins have been proposed as a mechanism to explain the complications of diabetes. Chronic hyperglycemia leads to the formation and accumulation of AGEs that may be a primary contributor to diabetic microvasculopathy. AGEs form on the amino groups of proteins, lipids, and DNA with complex cross-links and lead to modification in the structure and function of proteins. Formation of AGEs may directly damage the cells by impairing the function of a variety of protein both extracellular and intracellular. The cellular effects of AGEs is also mediated by its binding to receptors, namely receptor for AGE (RAGE) are attached to the foot plates of Muller cells. When activated they can initiate a cascade of signal transduction involving at least p21, p44/p42 mitogen activated protein kinase(MAPK) Nuclear factor kappaB(NF-kB) and protein kinase C which further lead to cellular damage. Upregulation of VEGF is seen in Muller cells along with increased expression of glial fibrillary acidic protein (GFAP), which causes increased reactive gliosis, when RAGE is activated.
3. **Reactive oxygen intermediate theory**

The byproducts of oxidative phosphorylation includes free radicals such as superoxide anion, whose production is increased by high levels of glucose. Free radicals not only damage the cellular proteins, it also reduces nitric oxide levels, promotes leukocyte adhesions to the endothelium and decreases the barrier function of endothelial cells. Oxidative stress can also activate PKC by increasing the formation of diacylglycerol.

4. **Protein kinase C theory**

Activation of PKC by phorbol esters is associated with increased permeability in epithelial and endothelial culture cells. It seems that certain PKC isoforms may play an important role in VEGF induced vasopernmeability. PKC inhibitors specific for the PKC-b isoform have been shown to significantly reduce VEGF-induced fluorescein leakage.

5. **Insulin receptors and glucose transporters**

There are at least 5 different types of facilitated cell membrane glucose transporters designated GLUT 1, GLUT 2, GLUT 3, GLUT 4 and GLUT 5 that appear to be the most important for the intracellular transport of glucose in the tissues like retina that do not require insulin. Of these GLUT 1 appears to be most prevalent in the retina, occurring in the microvascular and macrovascular endothelial cells and on RPE cells as well as in the Muller cells. These up regulations of the cell membrane glucose transporters could be a mechanism that initiates glucose mediated damage by permitting a much greater influx of glucose into cells.

6. **Vascular endothelial growth factors:**

VEGF-A belongs to a gene family that includes placental growth factor (PGF), VEGF-B, VEGF-C, and VEGF-D. VEGF-A recently has come to be accepted as one of the most potent factors inducing angiogenesis. Six major isoforms exist: 121, 145,165, 183, 189, and 206. VEGF-A is a ligand for two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, both of which act through downstream signalling cascades. VEGF-A, especially the VEGF-165 isoform, is emerging as an important factor in the pathophysiology of DME. VEGF is produced by RPE cells, ganglion cells, Muller cells, pericytes, endothelial cells, glial cells, neurons and smooth muscle cells of the diabetic retina. Up regulation of VEGF by hypoxia occurs in all of these cell types. Muller cells are the most important source of VEGF in the retina due to their high rate of glycolysis. VEGF produces conformational changes in the tight junctions of retinal vascular endothelial cells. VEGF induces phosphorylation of the tight junction proteins, occludin and ZO-1, which leads to increased vascular permeability by phos-phorylation of adherent junction and cytoskeletal proteins of vascular endothelial cells and induction of fenestrations in endothelial cell membranes. VEGF also may be associated with the early inflammatory changes seen with diabetic retinopathy and DME. In early diabetes, vitreous levels of VEGF are elevated.

7. **Other vasoactive substances**

There are other vasoactive substances like histamine, Angiotensin II, Matrix meta-lloproteinase, Pigment epithelium derived growth factor, Platelet derived growth factor and basic fibroblast growth factor also play an important role in the pathogenesis of diabetic macular edema.

### Anatomical and histological changes responsible for pathogenesis of diabetic macular edema

1. **Loss of pericytes:**

Loss of pericytes is one of the earliest and most specific signs of diabetic retinopathy. Pericytes are contractile cells that play an important role in the microvascular autoregulation. Loss of pericytes leads to alteration of vascular intercellular contacts and impairment of blood retinal barrier. Loss of intercellular contact also appears to promote endothelial cell proliferation resulting in the development of microaneurysms. Two major theories that have been implicated for the loss of pericytes are aldose reductase pathway and the platelet derived growth factor beta.

2. **Capillary basement membrane thickening**

Electron microscopic findings in diabetics show thickening of the capillary basement membrane along with deposition of fibrillar collagen and Swiss cheese vacuolisation of the otherwise homogenous pattern of the basement membrane collagen. Biochemical reactions like aldose reductase pathway, sorbitol pathway and enzymatic or nonenzymatic glycation of the basement membrane collagen have been play important role in the thickening of the basement membrane.

3. **Break down of the blood retinal barrier**

Break down of the blood retinal barrier is an important pathologic factor responsible for the development of diabetic macular edema. One mechanism by which there is a breakdown of the blood retinal barrier is opening of...
the tight junctions, also known as zonula occludens between the vascular endothelial cell processes. VEGF also plays an important role in the breakdown of the inner blood retinal barrier by altering the endothelial cell tight junctions. The other mechanism involved the increase in the vascular permeability is kallikrein kinin system through the production of bradykinin which in turn causes vasorelaxation of the retinal arterioles via nitric oxide.

4. Vitreoretinal interface

Clinical and anatomical evidence indicates that abnormalities in the structure of the vitreo retinal interface may play an important role in the pathogenesis of DME. DME may be exacerbated due to persistent vitreomacular traction by the residual cortical vitreous on the macula after PVD, thickened and taut posterior hyaloid that may or may not be adherent to ILM, macular traction due to tractional proliferative membranes, or loculation of cytokines in the pre-macular vitreous pocket. A diabetic retina compromised due to microvascular abnormalities may be vulnerable to increased exudation in the presence of any macular traction.

Classification of diabetic macular edema

The Early Treatment Diabetic Retinopathy Study (ETDRS) defined DME as retinal thickening or presence of hard exudates within 1 disk diameter of the center of the macula. To characterize the severity of macular edema and for treatment guidelines, the term clinically significant macular edema (CSME) is used. Macular edema is clinically significant if one of the following conditions is present: retinal thickening at or within 500 µm of the center of the macula and/or hard exudates at or within 500 µm of the center of the macula if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disk area in size, at least part of which is within 1 disk diameter of the macular center. On optical coherence tomography the DME can be classified into central involving and noncentral involving macular edema based on the presence or absence of cystic spaces at the central fovea thereby increasing the central foveal thickness. It is important to differentiate DME into central involving or non central involving as the treatment protocol for each is different. (Figure 1a and b)

Extrafoveal foci of retinal thickening and hard exudates may not cause any symptoms or affect visual acuity but DME that involves or threaten the centre of the macula cause significant vision loss. In the ETDRS, the 3 year risk of moderate vision loss among untreated DME is around 32%. In focal CSME, discrete points of retinal hyperfluorescence are present on the FA due to focal leakage of micro-aneurysms. The discrete leaking microaneurysms are thought to cause retinal thickening. Commonly, these leaking microaneurysms are surrounded by circinate rings of hard exudates. The exudates are lipoprotein deposits in outer retinal layers. In diffuse DME, areas diffuse leakage are noted on the FA due intraretinal leakage from a dilated retinal capillary bed and/or intraretinal microvascular abnormalities (RMA), and/or (in severe cases) from arterioles and venules without discrete foci of leaking microaneurysms. There may be associated cystoid macular edema (CME). Cystoid macular edema results from a generalized breakdown of the inner BRB with fluid accumulation, primarily in the outer plexiform layer.

Management of diabetic macular edema

Diagnostic imaging techniques

1. Fundus fluorescein angiography

Fluorescein angiography is a standard method used to evaluate patients with DME that is sensitive for qualitative detection of fluid leakage. The DME can be classified as focal and diffuse with the help of fundus fluorescein angiography. It also helps us to diagnose macular ischemia. Fundus photography is an important tool to look for the progression of the retinopathy in individual patients.
2. Optical coherence tomography

OCT has been used for high-resolution imaging of the retina and detection of increased retinal thickness. OCT has several advantages as a retinal imaging technique: 1) it is non-invasive (no injected dye involved) and well tolerated (especially important in children); 2) it provides quantitative information regarding retinal thickness with a high degree of accuracy and reproducibility; 3) it clearly reveals the presence and extent of vitreomacular traction. As shown by Chan and Duker, central macular thickness on OCT is a highly useful method for evaluation and comparison of the different therapeutic modalities for DME.

Treatment

Systemic therapy for DME

The main aims of systemic therapy in DR/DME are to reduce the risk of diabetic patients developing these conditions in the first place and to reduce the risk of progression of existing retinopathy or maculopathy to more severe, sight-threatening forms.

Modifying metabolic control

Improving glycemic control and lowering the level of glycosylated hemoglobin (HbA1c) is, at present, the most effective medical treatment to slow the progression of DR. This was proven by the Diabetes control and complications trial (DCCT) in type 1 diabetics and the United Kingdom prospective diabetes study. As per DCCT there was a 35%-40% reduction in the risk of retinopathy progression for every 10% decrease in HbA1C. According to UKPDS for every percentage point decrease in HbA1C there was a 35% decrease in the risk of microvascular complications. Intensive glycemic control was found to have effects that persist well beyond the course of treatment. The DCCT and UKPDS established optimizing metabolic control as a priority and led to the suggestion that it should be implemented early and maintained for as long as is safely possible. Although, the intensive control arm of the Action to Control Cardiovascular Risk in Diabetics (ACCORD) study was stopped because of increased all-cause mortality in people whose glucose was extremely tightly controlled with insulin and multiple oral agents.

Modifying hypertension

Hypertension is a major risk factor for DR and DME. The UKPDS demonstrated that control of blood pressure (systolic blood pressure <150 mmHg) led to a reduction in the progression of diabetic retinopathy and reduced need for laser treatment in the tight blood pressure control group compared with the less tight control group. More intensive blood pressure control resulted in a 37% reduction in the microvascular complications of DM.

Lipid lowering agent

Lipid lowering agents may decrease the risk of vision loss in patients with DR. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study on the effects of long-term fenofibrate on cardiovascular events in patients with type 2 diabetes found beneficial effects on microvascular complications that included DR. There were significant benefits in terms of the requirement for first laser and development of DME. The ACCORD-Eye study confirmed the results of the FIELD study. In ACCORD-Eye, the addition of fenofibrate to basal statin therapy resulted in a significant reduction in the progression of retinopathy, in a similar manner to that observed with intensifying blood glucose control, but with a good safety profile and without increasing the risk of hypoglycemia.

Ocular therapy for diabetic macular edema

Laser therapy

The ETDRS study was designed to evaluate the effects of argon laser photocoagulation for macular edema in a prospective, randomized, multicentre clinical trial. At 3 years, eyes with mild or moderate NPDR with macular edema at baseline treated with immediate focal/grid laser photocoagulation showed an approximately 50% decrease in the rate of moderate vision loss. Study done by DRCR.net compared the efficacy of modified ETDRS grid with mild macular grid in DME. In mild macular grid mild widely placed burns throughout the macula, both in the thickened and non thickened areas. At 12 months after treatment, the MMG technique is less effective at reducing OCT measured retinal thickening than the more extensively evaluated current modified ETDRS laser photocoagulation approach. However, the visual acuity outcome with both approaches is not substantially different. Since the advent of anti-VEGFs the role of focal laser in DME is decreasing although the efficacy of modified ETDRS grid in non central involving DME had been studied by DRCR.net. Focal/grid laser in these non-CI eyes was associated with relatively stable visual acuity and retinal thickness measurements, and decreased fluorescein leakage area at 1 year. Focal or grid laser can cause a scotoma within 20° of the central fixation, choroidal neovascularisation and subsequent fibrosis.
Pharmacotherapy for DME

Although it has been the mainstay of DME treatment for decades, laser monotherapy has some important limitations. Intravitreal injections of anti-VEGF agents have recently replaced ETDRS-style macular laser as the choice for initial treatment of center-involving DME, likely based on the results of several well-controlled randomized clinical trials. In recent DRCR.net reports, treatment with modified ETDRS laser resulted in stable or improved vision in a majority of patients, but close to 20% of patients lost >10 letters of visual acuity\(^{46,47}\). The efficacy of anti VEGF like ranibizumab, bevacizumab and aflibercept has been studied in different studies done by DRCR.net.

(a) Ranibizumab

Ranibizumab is an affinity–purified humanized monoclonal antibody fragment (Fab) that binds all VEGF A isoforms. It is a smaller molecule and has a molecular weight of 48 kilodaltons. The antiangiogenic effects of ranibizumab was first proven in wet age related macular degeneration by ANCHOR and MARINA studies. Following these studies, were done to prove the efficacy of ranibizumab in DME especially in central involving DME. DRCR.net evaluated intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of diabetic macular edema (DME)\(^{48}\). The 1-year mean change (±standard deviation) in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9±11, \(P<0.001\)) and ranibizumab + deferred laser group (+9±12, \(P<0.001\)) but not in the triamcinolone + prompt laser group (+4±13, \(P=0.31\)) compared with the sham + prompt laser group (+3±13). Reduction in mean central subfield thickness in the triamcinolone + prompt laser group was similar to both ranibizumab groups and greater than in the sham + prompt laser group. In the subset of pseudophakic eyes at baseline (\(n=273\)), visual acuity improvement in the triamcinolone + prompt laser group was similar to both ranibizumab groups and greater than in the sham + prompt laser group. In the subset of pseudophakic eyes at baseline (\(n=273\)), visual acuity improvement in the triamcinolone + prompt laser group appeared comparable to that in the ranibizumab groups.

No systemic events attributable to study treatment were apparent. The expanded 2-year results reported herein are similar to results published previously and reinforce the conclusions originally reported, that ranibizumab should be considered for patients with DME\(^{49}\). The RISE and RIDE study also the treatment protocol for use of intravitreal ranibizumab in central involving DME\(^{51}\). The treatment protocol as described by DRCR.net is shown below in figure 2. Intravitreal ranibizumab (0.5 mg/0.05 ml) treatment has to be started in patients with a central involving macular edema with increase in central foveal thickness(>250 µm) or visual acuity less than 20/32. The underlying rationale of the DRCR.net treatment algorithm for DME with intravitreal ranibizumab therapy requires monthly injections until an eye reaches “success” (the macular edema resolves or vision reached 20/20 or better); or until additional treatment is judged unlikely to be beneficial because of “no further improvement” compared with the previous visit(s) (edema improved after initiation of treatment, but eventually stabilized without reaching “success”); or an eye meets “failure” criteria (edema worsened or remained unaffected by treatment). Once ranibizumab is withheld, treatment could be resumed if macular edema recurs or worsens. If treatment is withheld and edema does not recur or worsen, the follow-up time could be doubled and if edema still does not recur or worsen, follow-up could be doubled again according to the study protocol. If macular edema persisted or was not improving despite anti-VEGF treatment additional focal/grid laser can be added as often as every 4 months\(^{51}\).

The randomised study done by DRCR.net for the efficacy of ranibizumab has also reported 3 cases on endophthalmitis and one case of progression of tractional retinal detachment\(^{48}\).

The most common side effects in clinical trials were conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure, and intraocular inflammation. There is a theoretical risk for arterial
thromboembolic events in patients receiving VEGF-inhibitors by intravitreal injection.

(b) Bevacizumab

Bevacizumab is a full length humanised monoclonal antibody that binds all VEGF-A isoforms and is FDA approved for colorectal carcinoma, but is used off label in the eye. Compared to ranibizumab it is a larger molecule and has a molecular weight of 149 kilodalton. A phase 2 trial done by DRCR.net to provide data on the short-term effect of intravitreal bevacizumab for diabetic macular edema (DME)\textsuperscript{52}. The results demonstrate that intravitreal bevacizumab can reduce DME in some eyes, but the study was not designed to determine whether treatment is beneficial. A phase 3 trial would be needed for that purpose. The BOLT study demonstrates that at 12 months of follow up the patients treated with intravitreal bevacizumab has a significantly better mean change in visual acuity than in the laser group\textsuperscript{53}.

The adverse affects are similar to ranibizumab although as per CATT trial some nonfatal adverse effects like GI bleeding were more in cases of bevacizumab\textsuperscript{54}.

(c) Aflibercept

Vascular Endothelial Growth Factor Trap-Eye is a 115-kDa recombinant fusion protein comprising the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1\textsuperscript{55}. Vascular Endothelial Growth Factor Trap-Eye is a panisoform VEGF-A inhibitor whose binding affinity to VEGF is substantially greater than that of either bevacizumab or ranibizumab\textsuperscript{55}, leading to a mathematical model predicting it could have substantially longer duration of action in the eye\textsuperscript{56}. In addition, VEGF Trap-Eye binds placental growth factors 1 and 2, which have been shown to contribute to excessive vascular permeability and retinal neo-vascularization\textsuperscript{57}.

The DA VINCI trial was done to show the efficacy, dosing and dosing schedule of aflibercept in DME\textsuperscript{58}. In this phase 2 clinical trial, all VEGF Trap-Eye doses and dosing regimens were found to be superior to macular laser photocoagulation for the treatment of DME over the course of 52 weeks and produced similar results in terms of preserving and improving visual acuity. Patients who received VEGF Trap-Eye benefited from significantly greater increases in mean visual acuity at 1 year (9.7 to 13.1 letters of improvement) compared with laser treatment alone (1.3 letters change). The average number of laser treatments administered to eyes randomized to VEGF Trap-Eye was fewer than 1 (of a maximum of 2 possible lasers), with most patients not requiring laser photocoagulation, indicating that the visual acuity and anatomic benefits achieved were the result of VEGF Trap-Eye and not laser treatment. The 2 mg dose of VEGF Trap-Eye almost completely eliminated vision loss at all dosing intervals. A prolongation of the retreatment interval from 4 to 8 weeks based on this data and the rationale of the improved binding properties of VEGF Trap-Eye represents an opportunity to potentially reduce the treatment and monitoring burden in anti-angiogenic therapy for DME\textsuperscript{59}.

(d) Combination therapy

As proven by the studies done by DRCR.net monotherapy with corticosteroids does not have much advantage over focal laser alone, several recent trials have provided good evidence to support combined treatment modalities for the treatment of DME. The RESTORE study was done to compare injection ranibizumab with laser treatment vs ranibizumab injection with sham laser vs laser alone\textsuperscript{60}. Although the visual gain and the improvement of macular thickness was more in both the ranibizumab groups than the only laser group, it failed to show an outright advantage of combination therapy over ranibizumab monotherapy. The READ 2 study also had similar results like RESTORE\textsuperscript{61}. At 2 years although both monotherapy and combination therapy with laser showed similar visual outcomes, the combination group required fewer treatments. Entry criteria for READ 2 were similar to the RESTORE study, but the READ 2 investigators chose to give injections every two months in the ranibizumab group. Importantly, in the combination group, patients received focal laser a week after injection, which differs from the RESTORE trial, which applied combined treatment on the same day. The DRCR.net's Protocol I study also investigated combination therapy involving ranibizumab or triamcinolone with focal laser\textsuperscript{62}. By three years, VA scores had improved more in the ranibizumab plus deferred laser group compared to prompt laser (9.7 letters vs 6.8 letters)\textsuperscript{63}.

(e) Intravitreal steroids

Corticosteroids have immune modulatory and antiangogenic properties and have been utilised for the management of DME. The major side effects of using intravitreal steroids are IOP rise and cataract formation. DRCR.net evaluated the efficacy and safety of 1 mg and 4 mg doses of preservative-free intravitreal triamcinolone in comparison with focal/grid photocoagulation for the treatment of diabetic macular edema (DME)\textsuperscript{64}. At 4 months,
a greater positive treatment response on visual acuity was seen in the 4 mg triamcinolone group compared with the other two groups. However, by 1 year, there was little difference in visual acuity between the groups, and at the time of the two-year primary outcome assessment, visual acuity and safety (with respect to intraocular pressure and cataract) were significantly better in the laser group than in either the 4 mg triamcinolone or 1 mg triamcinolone groups. There was no significant difference between the 1 mg triamcinolone and 4 mg triamcinolone groups in visual acuity at 2 years. Treatment group differences in the change in retinal thickening generally mirrored the effect on visual acuity, with initially a greater reduction in the 4 mg triamcinolone group, an eventual greater reduction in the laser group, and no difference between the two triamcinolone groups at 2 years. Results in a subset of randomized subjects who completed the 3-year follow-up are consistent with previously published 2-year results and do not indicate a long-term benefit of intravitreal triamcinolone relative to focal/grid photocoagulation in patients with diabetic macular edema similar to those studied in this clinical trial. Thus 1st line intravitreal triamcinolone is not recommended.

(f) Posterior subtenon triamcinolone:
DRCR.net also provided the pilot data on the safety and efficacy of anterior and posterior subtenon injections of triamcinolone either alone or in combination with focal photocoagulation in the treatment of mild diabetic macular edema (DME). No clinically important effects on central retinal thickness or visual acuity were found with peribulbar injections of triamcinolone with or without follow-up focal photoagulation in comparison with focal photoagulation alone.

(g) Sustained release implants
Steroids offer the potential advantage of longer duration of action. Rather than repeated bolus delivery of steroid, sustained-delivery devices have undergone development and testing for treatment of macular edema.

In the FAME trial, investigators used fluocinolone acetone vitreous inserts (Iluvien, Alimera Sciences, Alpharetta, GA) to treat subjects with center-involving DME who had failed at least one prior macular laser. The investigators compared two doses of steroid (0.2 and 0.5 µg/day) to sham injections. Both treatment groups showed larger gains in VA compared to the sham group, with 4.4 and 5.4 letters gained at two years in the low and high-dose groups, respectively, compared to a gain of 1.7 letters in the controls. The differences were more pronounced in favor of the steroid group in patients with chronic DME of more than three years’ duration. Cataract progression was significant among steroid-treated patients.

The CHAMPLAIN and PLACID study demonstrates the efficacy of dexamethasone implant in refractory diabetic macular edema. In the CHAMPLAIN study, the investigators administered a single dexamethasone injectable implant (Ozurdex, Allergan, Irvine, CA) in a cohort of patients with refractory DME and prior vitrectomy. The PLACID study randomized eyes with central diffuse DME to treatment with dexamethasone implant combined with macular laser or to sham injection with macular laser.

Poor responders and treatment failure
Definite worsening or treatment failure is defined as persistent edema along with 10 or more letter worsening from baseline at any visit, or, after at least 1 year of treatment, there was no improvement from baseline in central subfield thickness or visual acuity in the setting of “complete” laser. “Complete” laser was defined as direct treatment to all micro-aneurysms within areas of macular edema and grid treatment already applied to all other areas of macular edema. Once “failure” criteria were met, anti-VEGF treatment could be discontinued and any alternative treatment (such as intravitreal corticosteroids) along with focal laser could be performed.

In cases of treatment failure we obtain wide field angiography to assess peripheral and macular nonperfusion. Based on anecdotal evidence of peripheral ischemia driving persistent DME, we consider targeted PRP to areas of nonperfusion to reduce the ischemic burden. In those cases that remain refractory to treatment, the next step in the therapeutic algorithm is PPV with ILM removal. In eyes with significant ERM, or vitreous adhesion and VMT (figure-4), we often consider vitrectomy with peeling early in the course of treatment with adequate intravitreal pharmacotherapy in the perioperative period (Fig 3b). Study done by A. Kumar et al showed PPV with ILM peeling was beneficial by inducing a statistically significant reduction of macular thickness and macular volume. Visual acuity also demonstrated a trend towards improvement in both the ILM peel group and the grid laser group; however, the comparative VA outcome analysis between the two groups was not significantly different.

For poorly responsive patients, they should be evaluated
about 2 weeks after intravitreal injection and if there is some improvement of the macular thickness in the OCT, then monthly intravitreal anti VEGF injections can be continued along with focal laser photocoagulation. In pseudophakic patients we can consider treatment with intraocular steroids, either in bolus dose or sustained release implants.

DME with vitreomacular traction

Structural modification of diabetic vitreous occurs secondary to enzymatic and non-enzymatic collagen glycation. Accumulation of AGEs in the vitreous of hyperglycemic patients promotes collagen crosslinking and may be the cause of VMT in diabetic eyes. AGE accumulates along the posterior vitreous cortex and the ILM, where it may cause structural alterations that promote vitreoretinal traction. Vitrectomy to remove the posterior hyaloid and ILM may be beneficial in two ways: (1) by removing AGE ligand-induced mechanical traction between the posterior cortical vitreous and the ILM of macula; and (2) removal of AGEs may also inhibit the activation of the RAGE axis and its proinflammatory effects. Muller cells lie between the ILM and ELM and in close apposition with capillaries. In diabetic eyes, upregulation of VEGF in Muller cells may increase the vasopermeability of the retinal endothelial cells. The DRCR.net examined the role of vitrectomy and membrane peeling in the treatment of DME with a tractional component in a small, prospective cohort study. At six months postoperatively, VA improved by more than 2 lines in 38% of eyes. The mean decrease in macular thickness on OCT was approximately 160 µm, with 43% of patients having macular thickness of less than 250 µm.

Conclusions:

A holistic approach should be taken for the management of the patients of DME. The baseline systemic status of the patients should be evaluated with respect to the control of diabetes (HbA1C levels), hypertension, serum lipids and nephrological status.

A good ocular examination should be done by slit lamp biomicroscopy with a 90D and 78 D lens. Fundus fluorescein angiography is done to classify the type of macular edema and to rule out macular ischemia. A wide field fundus fluorescein angiography also helps to detect peripheral ischemia. OCT is done to classify the type of edema, to look for any interface abnormalities and also to follow up the patients.

In patients with non centre involving macular edema without any tractional elements identified on OCT. We often consider initial laser photocoagulation. We direct treatment at microaneurysms and other treatable lesions within the area of as per the modified ETDRS guidelines.
If the edema is center-involving, either intravitreal bevacizumab or ranibizumab has to be used. We also initially treat center-threatening diffuse edema with anti-VEGF injections along with laser treatment. In recalcitrant cases we can also use intravitreal steroids or sustained release implants especially in pseudophakic patients. In cases with vitreomacular interface abnormalities pars plana vitrectomy with ILM peeling should be considered.

We repeat biomicroscopic examination with ancillary diagnostic testing monthly to assess the patient's response to therapy. We continue anti-VEGF therapy with possible additional focal laser until macular edema resolves, until it becomes clinically nonsignificant, or until futility criteria are reached as in the DRCR.net's Protocol I.

**Summary of treatment**

- A detailed systemic evaluation has to be done to look for diabetes control, control of hypertension, hyperlipidemia and renal status.
- A diabetic patient presenting with diminution of vision or referred for screening should be clinically examined thoroughly to diagnose nonproliferative or proliferative diabetic retinopathy with or without DME.
- Fundus fluorescein angiography and optical coherence tomography has to be done to look for macular perfusion status and quantitative as well as qualitative analysis of the DME.
- A holistic approach should be taken to control the patient systemically.
- In cases of noncentre involving DME laser treatment has to be done. Laser of the thickened retina and direct treatment over the microaneurysms has to be done.
- In cases of centre involving DME, anti VEGF therapy has to be started and should be continued till either success criteria or the failure criteria are fulfilled.
- In cases of failure, complete laser or alternative treatment like intravitreal triamcinolone or sustained release implant should be used. Steroids are not recommended as a first line therapy as triamcinolone has not been found to be superior to laser therapy.
- In cases of vitreomacular DME or recalcitrant DME, a pars plana vitrectomy with vitreomacular traction release with ILM peeling should be done.

**References**


61. Nguyen QD, Shah SM, Heier JS, et al. Primary end point (six months) results of the Ranibizumab for


