Diabetic Macular Edema

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Introduction
Over the last one decade the management of diabetic macular edema has undergone a paradigm change.1 This is attributed to the newer diagnostic tests and pharmacological agents. There are enough good randomized controlled trials to prove the efficacy of these drugs. However, in clinical practice, there are many situations where the application of the findings of these clinical trials is often difficult. The aim of this article is to have a consensus statement on initial workup, diagnosis and management of diabetic macular edema.

Initial assessment of diabetic macular edema

History
- History regarding duration of diabetes, past glycemic control (hemoglobin A1c), Medications (especially insulin, oral hypoglycemics, antihypertensives, and lipid-lowering drugs), systemic history (e.g., renal disease, cardiovascular events, systemic hypertension, serum lipid levels, pregnancy).
- History related to drugs causing macular edema (Thiazolidinediones, fingolimod (used in MS), tamoxifen, taxanes, niacin, interferons and prostaglandin analogs).2–8

Ocular examination
- Detailed patient assessment should include a complete ophthalmic examination, including visual acuity (preferably by a ETDRS/Log MAR chart) and the identification and grading of severity of DR and presence of DME for each eye.9

Investigations

OCT
- All patients with DME should undergo OCT (Both Raster and radial scans). Retinal thickening (Central subfield and inner ETDRS ring thickness measurement), presence of vitreomacular adhesion or traction and morphological features like presence of neurosensory detachment, cystic spaces, foveal contour should be noted.
- The features suggestive of prognosis-like horizontal and vertical extent of IS-OS disruption, ELM disruption and hyper reflective foci (HFs) within the neurosensory retina should be noted. However, in presence of gross cystoid macular edema, often it is difficult to assess these features.10

Fundus fluorescein angiography
- Desirable to have baseline FFA done in all cases with DME. If otherwise contraindicated, at least a baseline fundus photo (ETDRS 7 Field) should be done.
- Preferably in cases where vision loss is disproportional to clinical picture (ischemic maculopathy), in cases where there is a suspicion of neovascularization, in cases of mixed retinopathy and those who are non-responders to treatment.
- Avoided in pregnancy, patients with history of serious adverse events during previous FFA and patients with allergy to fluorescein and severely impaired renal function.

Systemic
- Monitor fasting and post-prandial sugars, past glycemic control (hemoglobin A1c), Blood pressure and lipid profile (preferable in patient presenting with extensive exudates at macula) anemia and Renal function tests (Blood urea creatinine and microalbuminuria/albuminuria).11,12
- Either access the patients recent records/ask the patient to get these tests done and show to his treating physician/or order the investigations and then appropriately refer to physician.

Center-involving and non-center involving diabetic macular edema

Assessment: clinically by Slit lamp biomicroscopy and by SD-OCT

Center involving DME

Clinically: On clinical examination, definite retinal thickening due to diabetic macular edema involving the center of the macula.

On SD-OCT
- Loss of foveal contour
- Cystic space involving center of fovea.
- Neurosensory detachment involving the center of fovea
- Retinal thickening on SD OCT: central subfield thickness on OCT >290 μm for women, >305 μm for men.13

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Preferred Practice Pattern

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μm in men on spectral domain OCT (Zeiss cirrus). Heidelberg spectralis: ≥305 μm in women, and ≥320 μm in men.13

Must check the accuracy of OCT scan by ensuring it is centered and of adequate quality (for Zeiss Stratus, standard deviation of center point thickness should be ≤10% of the center point thickness and signal strength should be ≥6).

Non-center involving DME

Clinically: On clinical examination, definite retinal thickening due to diabetic macular edema within 3,000 μm of the center of the macula but not involving the center of the macula.

On SD-OCT

Cystic spaces and/or retinal thickening in non-central macular subfields

Center and non-center involvement in CSME

CSME is a form of DME that was precisely defined by the ETDRS as any of the following criteria being met14:

1 Any retinal thickening within 500 μm of the center of the macula.
2 The presence of hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina (not residual hard exudates remaining after the disappearance of retinal thickening)
3 A zone, or zones, of retinal thickening 1 disk area or larger, any part of which is within 1 disk diameter (1 disc = 1500 μm) of the center of the macula.

Criterion 1: Center involving; Criterion 2 and 3: non-center involving

Management of Diabetic macular edema

Situation 1: Non-center involving macular edema

Laser according to the ETDRS guidelines14,15:

• Focal photocoagulation: treatment of individual microaneurysms that fill with fluorescein and/or leak, as well as other points of leakage such as intraretinal microvascular abnormalities.

• Optional: treatment of microaneurysms (or punctate hemorrhages) <125 μm in longest diameter that did not fill with fluorescein; leaks within hemorrhages; treatment of microaneurysms or other focal points of leakage in the retina further than 2 DD from the center of the macula.

• Avoid: treatment of nerve fiber layer retinal hemorrhage (flame or splinter hemorrhage) and blot hemorrhage >125 μm in size.

• Grid laser treatment of areas of thickened retina showing diffuse fluorescein leakage and/or capillary dropout.

Situation 2: Non-center involving macular edema with few cystic spaces involving fovea (minimal center involvement)16

• If the vision is compromised, intravitreal anti-VEGF can be the treatment of choice
• If good vision (6/6), asymptomatic: laser according to the ETDRS guidelines
• If symptomatic and vision is good (6/6): intravitreal anti-VEGF

Situation 3: Center involving macular edema converting to non-center involving macular edema after intravitreal injections

• During monthly follow-up after anti-VEGF treatment the visit in which the edema becomes non-center involving, laser according to the ETDRS guidelines can be done. However, the follow-up visits after anti-VEGF injections should be continued as usual.

Situation 4: predominantly non-center involving macular edema (ring of circinates) after intravitreal injections or laser with plaque of hard exudate and normal foveal contour

• Control of systemic status (serum lipids), referral to physician to initiate lipid lowering drugs. Intravitreal steroids (1st Choice) can be considered after assessing the risk (Glaucoma). Laser may aggravate subfoveal deposits and should be avoided.17

Situation 5: treatment naïve center—involving macular edema

Anti-VEGF therapy is the first line of treatment for all DME patients without traction but with central involving macular edema. On monthly follow-up, look for Visual acuity and OCT for improvement.

• OCT and/or vision shows improvement: continue the treatment with anti–VEGF
• OCT shows progressive improvement but vision not improving: continue anti-VEGF, but consider angiogram to look for ischemia at 3 months.
• Vision improving but no OCT improvement: continue the treatment with anti–VEGF. Can consider adding laser, also look for VMA.
• No improvement on OCT and no visual gain: At 3 months, consider angiogram and then plan rescue treatment. Either switch to other...
anti-VEGF agent or consider steroid or consider adding laser.

When to stop injections:

- ‘Success’: vision improved to 6/6 and on OCT, return to normal foveal contour with reversal of thickening, disappearance of cystic spaces and NSD.
- ‘No further improvement’ Defined as <10% decrease in central subfield thickness and <5 letter increase in visual acuity since the most recent injection and, in the opinion of the treating ophthalmologist, it seems unlikely that additional treatment would provide any further benefit.

Once injections are stopped, close monitoring (at least every 3 months) with either an as-needed or a ‘treat and extend’ treatment approach should be done.

Retreatment should be considered in any case that involves significant fluid reappearence. However, clinical judgment is required.

When to switch to other agents

Patients with progressive worsening of vision over three consecutive visits in the presence of active DME (i.e., when other causes of vision loss have been excluded) can be considered as non-responders.

Situation 6: Previously treated center—involving macular edema with multiple Anti-VEGF injections/ Steroid injections/laser

- Stable: Control of systemic factors and follow-up based on time of last injection.
- Resistant: Evaluate with FFA and OCT.
  ✓ Identify the ETDRS treatable lesions [retinal microaneurysms located between 500 and 3000 μm from the foveal center, retinal microaneurysms located between 300 and 500 μm from the foveal center causing persistent CSME despite first laser treatment, areas of diffuse retinal leakage that could arise from microaneurysms, dilated capillary bed or intraretinal microvascular abnormalities and thickened ischemic zones] and treat if present.
  ✓ Carefully evaluate the follow-up protocols and response of previous treatments. Try to find out which treatment had the best response. Initiate the treatment with the same pharmacological agent and follow-up closely.
  ✓ Evaluate the systemic control of Diabetes, lipids, hypertension. Assess the renal status. Refer to a physician for adequate control.
- Recurrent: evaluate with FFA and OCT. Treat according to center involvement. Treat with drug which had shown good response previously. Evaluate the systemic factors for recurrence.

Situation 7: Proliferative diabetic retinopathy with macular edema

- If no traction: complete Pan retinal photocoagulation along with anti-VEGF and then subsequent management of macular edema according to the protocol.
- In presence of vitreous hemorrhage with hazy view of retina with suspected diabetic macular edema: PRP to the extent possible and pharmacological agents.
- In the presence of extramacular traction: PRP with burns 2 DD away from TRD, macular edema can be treated as usual protocol.
- In the presence of traction threatening or involving fovea: vitrectomy is indicated.

Situation 8: center involving macular edema with vitreoretinal surface abnormalities

- Evaluate the vitreoretinal interface on OCT.
- Focal vitreomacular traction with macular edema: vitrectomy is the choice.
- Extrafoveal traction site(s) without traction at the vitreofoveal site: anti-VEGF treatment can be initiated, with a close watch at the extrafoveal traction site on follow-up. However, if the traction is significant, option of IVTA/Ozurdex can be considered.
- Broad adherent epiretinal membrane with retinal thickening (VMA): in presence of changes due to diabetic macular edema, cystic spaces, NSD, retinal thickening, diffuse leak on FFA: treat like center involving macular edema. However, these show a relatively poor response to pharmacological treatment.
- Broad adherent epiretinal membrane with retinal thickening with no associated DME changes as mentioned above and thickening attributable to ERM: If asymptomatic; needs observation with OCT on follow-up visits. However, if symptomatic and shows worsening on follow-up visits (drop in vision) can plan vitrectomy with epiretinal membrane removal. If planning vitrectomy the prognostic features which should be taken into account include initial visual acuity (poorer VA has poor prognosis), OCT features like IS-OS defects and breaks in ELM, FFA features like the presence of ischemia, and status of optic nerve (pallor).
**Situation 9: Center involving macular edema in pseudophakic eyes**

- Differentiating pseudophakic from Diabetic macular edema in presence of DR: diffuse petalloid type of leakage with disc leakage on the fluorescein angiogram and with very few aneurysms and no hard exudates around the macula is suggestive of pseudophakic macular edema.

- Presence of diabetic macular edema with no component of Irvine Gass: treat as center involving macular edema. However, if compliance is an issue one can initiate the treatment with intravitreal steroids.

- Presence of both diabetic macular edema and Irvine Gass: can plan treatment of diabetic macular edema along with non-steroidal anti-inflammatory drugs. If no contraindications, intravitreal steroids can be considered as an initial choice.

- Time to start treatment of DR in fresh pseudophakia: if macular edema is detected after cataract surgery, laser (macular) can be initiated after 1 month (after uncomplicated phacoemulsification); PRP if indicated can be done early (with indirect laser delivery or gentle slit lamp delivery after sterilizing the contact lens) and intravitreal anti-VEGF can also be planned after 1 month.

**Situation 10: Macular edema during pregnancy**

- Pregnancy may promote the onset of DR (in about 10% of cases) as well as contribute to its worsening when already present.

- The proliferative retinopathy must always be treated; treatment should be earlier in pregnant women compared to non-pregnant women.

- Pregnancy can also cause macular edema; it spontaneously regresses during postpartum and therefore does not require immediate treatment.

- However, if macular edema occurs early in the pregnancy and there is progressive deterioration of vision, laser/intravitreal steroids should be preferred and anti-VEGF avoided.

**Situation 11: macular edema in young type I diabetes**

- Management of DME in type 1 diabetes is similar to type 2; however, they need to be referred to their physician for optimal glycemic control.

- In cases of PDR with macular edema, there is an increased risk of thickened PHF contributing to edema. Clinical and OCT assessment of this is important.

**Situation 12: center involving macular edema in vitrectomized eyes**

- Pseudophakic eyes with center involving macular edema: intravitreal steroids should be considered as first choice in suitable cases.

- In presence of recurrent vitreous hemorrhage with center involving macular edema: anti-VEGF are the better choice.

- Selected cases where the risk of IOP spike and cataract is a concern: intravitreal anti-VEGF can be considered. Close monitoring of IOP and counseling of patient is important. Consider choosing dexamethasone over IVTA to reduce IOP spikes.

**Situation 13: ischemic macular edema**

- Access the ischemia with FFA and OCT
  - FFA: the minimum criterion for diagnosing macular ischemia is moderate FAZ irregularities. Moderate irregularities is defined as abnormally dilated and tortuous capillaries budding into the FAZ, terminal arterioles/venules directly abutting FAZ margins, and enlarged intercapillary spaces around the FAZ. The size is a minor criterion compared to the irregularity of FAZ. Ischemia was diagnosed only when the longest diameter of FAZ was ≥ 1000 µ (the measurements should be made digitally using a FF 450plus fundus camera [VISUPAC system, Carl Zeiss, Germany].
  - Severe FAZ irregularity is defined as the destruction of the FAZ architecture: grossly enlarged FAZ with ‘pruned off’ arterioles.
  - Normal FAZ is defined as an FAZ <1000 µ in the longest diameter, regular and round/horizontally oval in shape. Mild undulations of FAZ were also considered normal.

- Can also grade ischemia using ETDRS grading system, from 0 (normal), to 1 (questionable), 2 (less than half the original circumference destroyed), 3 (more than half the contour destroyed but some remnants remain), and 4 (capillary outline completely destroyed).

- Assessing ischemia on OCT: DME in presence of ischemia has retinal thickening in the outer retinal layers. Inner retinal layers, including the ganglion cell layer (GCL) and RNFL, are thinned.

- In FFA grade 1 and 2: treat as non-ischemic (Center and non-center involving)
• FFA Grade 3: avoid laser photocoagulation, can consider steroids in the presence of center involving macular edema

• FFA Grade 4: would not benefit from any treatment.

**Situation 14: center involving macular edema with history of recent stroke**

• If a patient had stroke (cerebrovascular accidents) or myocardial infarction, within last 3 months, do not initiate treatment with anti-VEGF. Treatment with laser or steroids can be considered in these patients.

• If the history is >3 months old, the treatment can be initiated with anti-VEGF. However, if systemic risks of thromboembolic phenomenon are significant, it is best to consult a physician first.

**Situation 15: diabetic macular edema in glaucomatous eyes**

• In eyes with established glaucoma/glaucoma suspect/ocular hypertension: avoid intravitreal steroids. Even if intravitreal anti-VEGFs are used, monitoring of IOP and if required augmentation of anti-glaucoma medications is required.

• For rescue treatment in this group, laser photocoagulation is preferred.

**Situation 16: considering diabetic macular edema for vitrectomy**

• Focal vitreomacular traction: vitrectomy is the choice.

• Broad vitreoretinal adhesion: if anti-VEGFs and rescue treatment have failed to resolve the macular edema and the ophthalmologist feels that there is a scope of improvement, vitrectomy can be considered.

• Diffuse diabetic macular edema: if does not show desired outcome after primary and rescue treatment, can be considered for vitrectomy with or without ILM peeling. Patients vision, optic disc status, and macular perfusion need to be evaluated first.

**Situation 17: Cataract with Diabetic macular edema**

• Diabetic macular edema with cataract: as long as there is a clear enough view to see DME clinically and on OCT treat DME according to the protocol. Once macular edema is treated, one can plan cataract surgery. Ideally we can wait for 3 months after cataract surgery.

• However, if the view is not good enough to treat DME, cataract surgery can be done either along with intravitreal anti-VEGFs, or 2 weeks after surgery and subsequent protocol continued.

• If the view is clear and treatment initiated, but even after three to four injections, the edema has not resolved; and during this time cataract has worsened: cataract surgery can be planned and treatment of DME continued thereafter. Can consider concurrent intravitreal injection or injection post-surgery based on logistics.

• If during treatment of DME, patient also develops PCO, NdYAG capsulotomy can be planned and treatment of DME can be continued as usual.

**Situation 18: diabetic macular edema with optic nerve abnormalities**

Differentiating NA-AION, papillopathy and papillophlebitis:

• NA-AION: the optic disc edema in NAION may be diffuse or segmental, hyperemic or pale, but pallor occurs less frequently than it does in AAION. A focal region of more severe swelling often is seen and typically displays an altitudinal distribution, but it does not correlate consistently with the sector of visual field loss. Diffuse or focal telangiectasia of the edematous disc may be present, occasionally prominent enough to resemble a vascular mass or neovascularization.

• Papillopathy: acute onset of unilateral or bilateral disc edema in usually in young, type 1 diabetics, sometimes even type 2 diabetes, without the usual defects in visual field and pupillary function associated with NAION or optic neuritis.

• Papillophlebitis: typically shows more prominent retinal venous congestion, peripheral retinal hemorrhages.

• In AION cases, FFA shows early disc hypofluorescence due to hypoperfusion with late leakage around the affected segment. However, in diabetic papillopathy cases the FFA shows a very early disc leakage that increases throughout the study. The early hyperfluorescence is most likely due to telangiectasia of the optic disc. Fields typically show altitudinal defect in NA-AION which are not seen in papillopathy.

• NA-AION with macular edema: differentiate whether the macular edema is due to Macular star seen in NA-AION or diabetic macular edema. FFA plays an important role. Identify the presence of DR lesions which can cause edema (MA, diffuse leak, IRMA). If it is due to diabetic macular...
edema, treat as either center involving or non-center involving. If it is due to NA-AION, treatment of NA-AION would resolve the edema, no treatment by intravitreal injections is required.

Papillopathy with diabetic macular edema: treat the macular edema as any other diabetic macular edema.

Papillophlebitis with macular edema: FFA to determine whether the macular edema is due to diabetes or vein occlusion. If due to diabetes, treat as any other diabetic macular edema. In these cases, one should rule out inflammatory causes as well.

**Situation 19: diabetic macular edema with anemia**

- In the majority of patients, the anemia is related to renal dysfunction and may require subcutaneous erythropoietin injections for treatment. The macular edema usually improves with it; however, one should keep a close watch on proliferative component, as erythropoietin can worsen the same.
- Anti-VEGF can be the preferred agent in presence of anemia and center involving DME.

**Situation 20: diabetic macular edema with mixed retinopathy**

- The management of diabetic macular edema remains unchanged; however, the history of cardiovascular risk factors should be sought and if required a physician consultation should be done.
- In cases of accelerated hypertension, anti-VEGF should be avoided.

**Situation 21: Diabetic macular edema with lattice degenerations**

A careful examination of the periphery, and prophylactic treatment of any lesions that could predispose to RD, is preferable. The gap between laser prophylaxis and the injection should ideally be 3 weeks.

**Challenges in any intravitreal injection among diabetics**

**Need for bilateral injection:** On many occasions there is a requirement of multiple Anti-VEGF injections in both eyes. Ideally a gap of a week or at least 3 days should be kept between both the eyes.

**Patient with non-healing foot ulcer:** This poses a risk of infection. Before injections make it sure the patient is in care of a surgeon/physician. The attendant and patient should be counseled to do foot dressing before doing ocular dressing or instilling the drops. In presence of active infection, intravitreal injections should be avoided. Look for non-invasive alternatives such as laser if feasible.

**Fluctuating glycemic control:** These patients pose a challenge for the treating physician, as before each anti-VEGF injection, the blood sugar has to be <200 mg%; fluctuating glycemic control can alter the compliance of regular intravitreal injections.

**Monthly follow-up:** As diabetics, often also have other co-morbid conditions which require regular care like nephropathy, cardiovascular problems, neuropathy etc.; regular monthly follow-up may not be feasible in some of them. If compliance is an issue, laser treatment can be considered.

**Conclusion**

Management of diabetic macular edema is a challenging situation; as in clinical practice we come across many combinations of phenotypes and clinical scenario. The choice and protocols of management may slightly differ; however, principles of treatment remain same. The clinical trials in the last decade with pharmacotherapy have largely helped in changing paradigms in management of DME.

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