

Diabetic macular edema treatment guidelines in India: All India Ophthalmological Society Diabetic Retinopathy Task Force and Vitreoretinal Society of India consensus statement

Sneha Giridhar, Lalit Verma¹, Anand Rajendran², Muna Bhende, Mallika Goyal³, Kim Ramasamy⁴, Rajalakshmi⁵, Padmaja R⁶, Sundaram Natarajan⁷, Mahesh Shanmugam Palanivelu⁸, Rajiv Raman, Sobha Sivaprasad⁹

Diabetic macular edema (DME) is a common cause of moderate visual impairment among people with diabetes. Due to the rising number of people with diabetes in India, the absolute numbers of people with DME are significant. There are several treatment options for DME, and the choice of treatment is based on the availability of retinal specialists and infrastructure for the delivery of treatment. A major challenge is the out-of-pocket expenditure incurred by patients as most treatment options are costly. Treatment also varies based on the associated ocular and systemic conditions. The All India Ophthalmology Society (AIOS) and the Vitreo-Retinal Society of India (VRSI) have developed this consensus statement of the AIOS DR task force and VRSI on practice points of DME management in India. The objective is to describe the preferred practice patterns for the management of DME considering the different presentations of DME in different clinical scenarios.

Key words: Consensus statement, diabetic macular edema, intravitreal anti-VEGFs, steroids

Diabetic retinopathy (DR) is the most common ocular complication of type 1 (T1DM) and type 2 diabetes (T2DM).^[1] Diabetic macular edema (DME) can coexist with any severity level of DR and is a cause of moderate visual impairment in people with diabetes.^[1] Multiple biological pathways triggered by hyperglycemia can alter the blood-retinal barrier and cause DME. Vascular endothelial growth factor (VEGF) plays a key role in the alteration of the blood-retinal barrier.^[2] In addition, inflammatory and tractional elements may complicate the pathogenesis of DME. In addition to clinical examination and fundus fluorescein angiography (FFA), optical coherence tomography (OCT) has become an important diagnostic tool in the diagnosis and management of DME.

A large variety of therapeutic strategies are now available to manage DME: macular laser photocoagulation, intravitreal

pharmacotherapy (anti-VEGF and steroids), and surgical intervention. Diverse approaches may be required to treat DME depending on the location, type, and associated morbidities and complications. This set of guidelines was developed to standardize the treatment options to avoid variations in the management of DME. A consensus from a Delphi survey and evidence base from randomized controlled trials were used to inform best practices in India.^[3] Considerations were given to out-of-pocket expenses incurred for the treatment and the compliance required for optimal treatment benefit. This review discusses the management of DME in different situations such as noncenter-involving macular edema (NCI-DME), center-involving macular edema (CI-DME), DME with other associated ocular problems, and DME with systemic comorbidities.

Evaluation of a patient with DME

A detailed ophthalmic examination should include the following information:

- Ocular and systemic history
- Visual acuity (LogMAR or ETDRS chart) for distance and near vision

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

Cite this article as: Giridhar S, Verma L, Rajendran A, Bhende M, Goyal M, Ramasamy K, *et al.* Diabetic macular edema treatment guidelines in India: All India Ophthalmological Society Diabetic Retinopathy Task Force and Vitreoretinal Society of India consensus statement. *Indian J Ophthalmol* 2021;69:3076-86.

Access this article online

Website:
www.ijo.in

DOI:
10.4103/ijo.IJO_1469_21

Quick Response Code:



Shri Bhagwan Mahavir Vitreoretinal Services Sankara Nethralaya, ²Retina-Vitreous Services, Aravind Eye Hospital Chennai, ³Department of Ophthalmology, Dr. Mohan's Diabetes Specialities Centre and Madras Diabetes Research Foundation, Chennai, ⁴Aravind Eye Hospital, Madurai, Tamil Nadu, ¹Centre for Sight, New Delhi, ³Retina-Vitreous and Uveitis Service, Apollo Health City, Jubilee Hills, ⁶Smt Kanuri Santhamma Centre for Vitreo Retinal Diseases, LV Prasad Eye Institute, Hyderabad, Telangana, ⁷Aditya Jyot Eye Hospital, Mumbai, Maharashtra, ⁸Sankara Eye Hospital, Bengaluru, Karnataka, India, ⁹NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hosp NHS Foundation Trust, London, UK

Correspondence to: Dr. Rajiv Raman, Senior Consultant, Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18, College Road, Nungambakkam, Chennai - 600 006, Tamil Nadu, India. Email: rajivpgraman@gmail.com

Received: 31-May-2021

Revision: 28-Jun-2021

Accepted: 20-Aug-2021

Published: 29-Oct-2021

- C. Fundus examination (with 90D/78D/Indirect Ophthalmoscopy)
- D. Color fundus photography (posterior pole and 4-field or wide-field)
- E. Fundus fluorescein angiography (FFA) at baseline to provide the overall and macular capillary nonperfusion (CNP)
- F. Optical coherence tomography (OCT)
- G. Optional - Optical coherence tomography angiography (OCTA) may be done to rule out macular ischemia.

Ocular and systemic history

The duration of diabetes, control of hypertension, hyperglycemia, and hyperlipidemia should be recorded.^[4,5] Anemia and renal disease are other factors associated with DME. Detailed drug history is essential as drugs such as thiazolidinediones, tamoxifen, taxanes, niacin, interferons, and prostaglandin analogs can cause macular edema. Discontinuing these drugs may be useful if permitted by the physician. History of recent surgical procedures should be kept in mind to rule out pseudophakic cystoid macular edema. A detailed history regarding systemic comorbidities should be taken as these alter the course of the disease and treatment response.

Visual acuity

To assess disease progression and treatment response, best-corrected visual acuity (BCVA) must be done, preferably using a LogMAR or Early Treatment for Diabetic Retinopathy Study (ETDRS) chart. Baseline BCVA provides the starting visual acuity (VA) of a patient, and it is important to assess whether BCVA correlates with the DR and DME status. Other causes of impaired VA should be considered, with refractive errors and cataract being common causes. (Please see ocular comorbidities for more details.)

Fundus examination

Diagnosis of DME can be assessed by means of fundus biomicroscopy following pupil dilation.^[6] A thorough stereoscopic slit-lamp biomicroscopic examination of the posterior pole (with +90D or +78D lens) should suffice to detect thickening of the macula in a patient with diabetes. On slit-lamp biomicroscopy, DME is defined as the presence of any retinal thickening within 2 disc diameters of the center of the macula. Based on the ETDRS, DME is further classified in an attempt to identify DME that would benefit from macular laser photocoagulation.^[6] Macular laser photocoagulation is done in eyes with clinically significant macular edema (CSME). Fig. 1 shows the definitions of stages of DR, CSME, and OCT classification of DME as CI-DME and NCI-DME.

It is recommended to have a slit lamp evaluation, intraocular pressure check, and assessment of pupillary response by a trained person before dilatation of pupil for fundus examination. The first step is to characterize the stage of DR.

Color fundus photography

The clinical examination is preferably documented by either a posterior pole and 4-field fundus photography or widefield photography. Severity of DR should be graded according to the International Classification of Severity of Diabetic Retinopathy.

Eyes with proliferative diabetic retinopathy (PDR) are more prone to DME.

Fundus fluorescein angiography

It is important to do a baseline fundus fluorescein angiography (FFA) before planning laser treatment in DME. However, in cases where intravitreal injections (IVI) are planned for treating CI-DME, a baseline FFA is not required, unless it is indicated to ascertain the stage of DR or macular ischemia.

FFA classifies DME as focal, diffuse, or mixed edema. Focal edema is due to leaking microaneurysms; they may form a circinate pattern, and these benefit from focal macular laser. Diffuse DME is due to leakage from the macular capillary bed. Although grid laser was recommended by ETDRS (add reference) as a treatment for diffuse DME, it is best treated with anti-VEGF agents. FFA reveals the source of leakage as microaneurysms resulting in either focal, or often the circinate pattern edema, or leakage from retinal capillaries resulting in diffuse edema or areas of CNP or enlarged foveal avascular zone (FAZ). Macular capillary nonperfusion and enlarged FAZ are the signs of macular ischemia. However, FFA shows that the microaneurysms in the superficial capillary plexus with those in the deep capillary plexus can be visualized with OCTA, which is now becoming a part of clinical management of DME as it provides information CNP. Currently, it is challenging to assess CNP in the presence of DME due to poor segmentation in the presence of edema. However, after resolution of DME, the areas of CNP, especially in the deep capillary plexus, may provide clues on visual prognosis or explain lack of improvement of VA following treatment of DME due to concomitant diabetic macular ischemia.

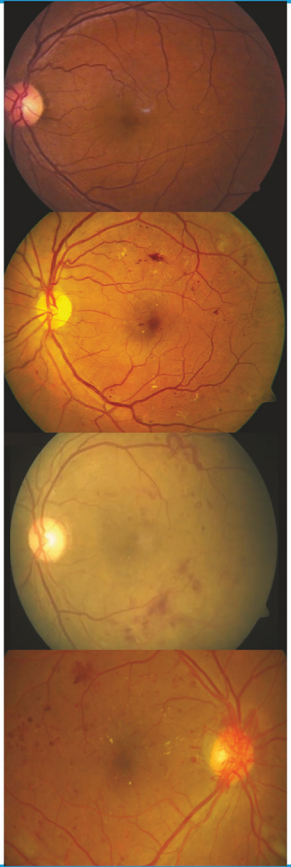

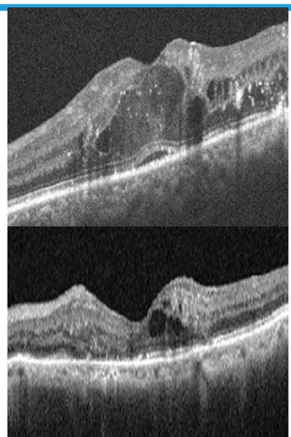
Optical coherence tomography (OCT)

With the advent of OCT and anti-VEGF agents, the focus of classifying DME has shifted to OCT evidence of DME involving the central subfield zone of the ETDRS grid termed center-involving DME (CI-DME) or noncenter-involving DME (NCI-DME). DME is diagnosed as intraretinal and/or subretinal hyporeflective spaces on OCT. Although several morphological features have been investigated as prognostic factors of DME, hyperreflective foci,^[5] loss of integrity of outer retina, and presence of disorganized inner retinal layers (DRIL) on OCT are well-defined as poor prognostic indicators. OCT is now widely used as an imaging tool to diagnose DME as assessment by fundus biomicroscopy is quite subjective. Both neurosensory detachment and tractional macular edema OCT are recommended if the grade of DR is more than moderate nonproliferative DR (NPDR). It is important to rule out tractional components in patients who are not responsive to pharmacotherapy.

Management of noncenter-involving macular edema (NCI-DME)

Treatment naïve NCI-DME

Any DME not involving the fovea is classified as NCI-DME.^[7] On OCT, the retinal thickening involves any 1 or more of the noncentral fields on the ETDRS grid. Retinal thickening is defined as above the threshold (>320 μm) and central subfield thickness (CST) of less than normal +2 SD (machine-specific). This subgroup of patients can present with good visual acuity. However, the progression of NCI-DME to CI-DME

<p>MILD NPDR Microaneurysms only</p> <p>MODERATE NPDR More than just microaneurysms but less than severe NPDR</p> <p>SEVERE NPDR Any of the following and no signs of proliferative retinopathy <i>More than 20 intraretinal hemorrhages in each of 4 quadrants</i> <i>Definite venous beading in 2 or more quadrants</i> <i>Prominent IRMA in 1 or more quadrants.</i></p> <p>PDR One or both of the following</p> <ul style="list-style-type: none"> • <i>Neovascularisation</i> • <i>Vitreous/ preretinal hemorrhage</i> 	
<p>Clinically significant macular edema (CSME)</p> <ol style="list-style-type: none"> 1. Retinal Thickening at or within 500µm from the centre of the macula. 2. Hard exudates, at or within 500µm from the centre of the macula, if there is associated thickening of the adjacent retina. 3. An area or areas of retinal thickening at least 1 disc area in size, a part of which is within 1 disc diameter of the centre of the macula 	
<p>Centre Involving DME(CI DME)</p> <p>Center involving DME (CI-DME) is diagnosed using SD-OCT when the central subfoveal thickness (CST) on the macular map is 305 or worse in women and 315 or worse in men on Heidelberg (or equivalent thicknesses on the other SD-OCT machines)</p> <p>Non Centre Involving DME(NCI –DME)</p> <p>Non-Center involving DME (NCI-DME) is diagnosed using SD-OCT when the central subfoveal thickness (CST) on the macular map is less than 305 in women and less than 315 in men on Heidelberg (or equivalent thicknesses on the other SD-OCT machines) with increased thickness in inner and outer ETDRS subfields.</p>	

NPDR: Non proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, IRMA: Intraretinal microvascular abnormalities, DME: Diabetic macular edema

Figure 1: Classification of diabetic retinopathy (DR), clinically significant macular edema (CSME), and optical coherence tomography classification of DME

in the first year is generally low (14%). Systemic factors such as hyperglycemia, hyperlipidemia, and hypertension are risk factors for progression to CI-DME, and all treating ophthalmologists should stress optimal control of these risk factors.

Treatment for naïve NCI-DME:

- NCI-DME with good vision (6/6-6/9) can be observed with monthly follow-up^[4]
- NCI-DME with BCVA <6/9 attributed to macular edema can be treated with macular laser if it meets the CSME criteria.^[4] Focal laser is performed targeting leaking microaneurysms shown on FFA in areas of thickening between 500–3000 µm from the center of macula.^[4]

Conventional argon laser is absorbed by the melanin pigments in RPE, leading to protein denaturation and atrophy. However, intense whitening of the retinal burns is best avoided. In subthreshold micropulse laser, energy is delivered in many repetitive short impulses. The laser power is set at a low level so that it does not form any visible lesion on the retina. It has alternating ON and OFF cycles. The “ON” time is 100 µs of micropulse power, and the “OFF” time is 1900 µs, which is without power and this gives time for the heated tissue to cool down.^[8,9] The subthreshold micropulse laser can be diode laser at 810 nm or yellow at 577 nm. Recent reports have also studied the use of 532-nm green lasers.^[10] Complications of conventional macular laser photocoagulation include progressive enlargement of the laser scar that may lead to foveal atrophy and choroidal neovascularization.^[8,9]

Clinical signs with poor visual prognosis that coexist with DME include subfoveal plaque, fibrosis and macular pigmentary changes, and these should be recorded and prognosis explained to the patient. Macular laser is unlikely to benefit in these situations and should only be done with caution.

NCI-DME after intravitreal injections for CI-DME

Patients may have persistent NCI-DME after treating CI-DME with anti-VEGFs or steroid therapy. BCVA plays an important role in decision-making.

- In eyes with BCVA of 6/9 or better, it is best to observe the patients on a 2 monthly basis. The follow-up can gradually be increased to a maximum of 4 months if vision stays stable and there is no progression to CI-DME.^[11,12]
- In eyes with BCVA worse than 6/9, macular laser (focal/grid laser) may be considered if it meets CSME criteria. These patients can then be followed up after a month with the follow-up interval then doubled to a maximum of 4 months.^[11-13] Those who fail to respond to macular laser can be planned for a repeat treatment with anti-VEGFs.^[14]
- A plaque of hard exudates may deposit at the macula, close to the fovea, which carries a poor prognosis, and this should be explained to the patient before embarking on any therapy. Intravitreal steroids (triamcinolone acetonide or dexamethasone) have been reported as an option to reduce the exudates, but its effects are equivocal.^[15,16] Potential risk of glaucoma and cataract (in phakic eyes) should be assessed prior to steroid injection. In the absence of macular thickening, repeat injection of anti-VEGF for persistent exudates may resolve the exudates, but improvement of

vision is unlikely.^[17] These patients should be evaluated for control of systemic status especially serum lipids and treated with lipid-lowering drugs as per the advice of the physician.

Management of center-involving diabetic macular edema (CI-DME)

Treatment of naïve CI-DME

Intravitreal injections (IVI) of anti-VEGF agents are the first line of treatment for naïve CI-DME.^[18] Multiple clinical trials have demonstrated that anti-VEGF therapy is more effective in improving vision in CI-DME than macular laser treatment, supplanting it as the first-line therapy for CI-DME.^[12,19,20] The standard doses for the IVI anti-VEGF pharmacotherapies are ranibizumab (Lucentis/Accentrix/biosimilar) – 0.5 mg/0.05 ml, bevacizumab (Avastin) – 1.25 mg/0.05 ml, and aflibercept (Eylea) – 2 mg/0.05 ml.

The Diabetic Retinopathy Clinical Research Network (DRCR) protocol for CI-DME starts with monthly IVI for 4–6 months initially and then allows for holding on treatment if there is no improvement in vision or central subfield thickness, or if 6/6 Snellen vision and/or the resolution of DME has been achieved. Anti-VEGF treatment can be resumed if there is a worsening vision or CST on subsequent visits. If on consecutive visits, treatment is not required, the follow-up interval is doubled up to 4 months. This approach has been demonstrated to reduce the number of injections while delivering excellent VA gains. Treatment is deferred when vision has improved to 6/6 and the OCT has become normal (normal foveal contour with reduction of retinal thickening at the macula, regression of the neurosensory detachment, and disappearance of cystic spaces in the neurosensory retina). An alternative approach to reducing the injection burden is a treat-and-extend regimen, wherein the interval between visits is adjusted based on the treatment response. A recent prospective trial showed that treat and extend approach is comparable in visual and anatomic results at 2 years to monthly dosing with fewer injections.^[21]

Stopping anti-VEGF therapy

No further improvement is defined as a <10% decrease in the central subfield thickness on OCT and a <1 line improvement in VA on the Snellen chart after the last injection, and in the opinion of the treating ophthalmologist, no further benefit can be expected with additional treatment.^[4] In eyes with vision better than or equal to 6/7.5 and persistent DME, treatment can be withdrawn and the patients kept under observation, reinstating treatment if DME recurs.^[22,23]

Recurrent DME

In eyes that develop recurrent DME after complete resolution following multiple anti-VEGF injections, it is preferable to continue the same treatment if vision continues to improve with a progressive decrease in CST.

Nonresponders to anti-VEGF therapy

The most common reason for nonresponse to anti-VEGF therapy is due to inadequate treatment as per the above protocol. In eyes with persistent DME and VA <6/12, a different anti-VEGF may be considered. If the patient has been on bevacizumab, a switch to ranibizumab or aflibercept is recommended; if on ranibizumab, a switch to aflibercept is advised. In eyes with suboptimal response, most ophthalmologists in the Asia Pacific

switch to another anti-VEGF agent after 2–3 injections and to steroids after 6 injections.^[24]

Intraocular steroids, preferably implants, can be considered in some situations and patients who have persistent DME despite anti-VEGF therapy might benefit from this treatment. The DRCR.net Protocol I and Protocol T have demonstrated the percentage of patients who continue to have macular edema after six months of treatment.^[25]

Switching to intravitreal steroids can be considered in the following situations^[26]:

1. Responding to anti-VEGFs but difficult to maintain frequent follow-up visits
2. Pseudophakic patients who have reached a plateau – persistent intraretinal fluid (IRF)/VA <6/12
3. Persistent edema and needing cataract surgery
4. Occurrence of systemic vascular event while on anti-VEGFs
5. Associated features such as extensive hard exudates and presence of hyperreflective dots on OCT^[27]
6. Eyes post vitrectomy.

Additional laser photocoagulation to treat persistent edema (considered after 4–6 injections may also be considered for the following:^[28]

1. Persistent CSME with visible microaneurysms
2. If a switch to steroid is not possible (glaucoma/young phakic patient), grid +/- focal laser may be applied to areas of retinal thickening.

However, the role of peripheral PRP for eyes with peripheral CNP in eyes with persistent edema despite the failure of all pharmacological therapy remains questionable.^[29,30]

Role of vitrectomy in DME

Patients with recalcitrant DME may benefit from vitrectomy surgery. These include DME with predominantly vitreomacular traction or tractional epiretinal membrane (ERM) or a taut posterior hyaloid.^[31] Through the removal of adherent posterior hyaloid, vitreomacular traction (VMT), and ERM, the anteroposterior and tangential traction is released, resulting in better oxygenation to the inner retina, which may improve capillary blood flow in the perifoveal area and reduce hypoxia-induced VEGF drive. In addition, histamine, VEGF, and free radicals have been shown to be decreased in the preretinal space after vitrectomy.^[32,33] An attached vitreous also has an adverse effect on the clinical response of DME.^[34] However, vitrectomy may result only in structural improvement with nonsignificant visual improvement.^[34,35] It is also hypothesized that following vitrectomy, the retinal pigment epithelial pump improves.^[36]

Studies also describe the role of peeling of the inner retinal membrane (ILM) in these eyes. The ILM contributes to tangential traction and helps prevent recurrences of ERM especially in cases of vitreoschisis. There is little evidence to support vitrectomy as a treatment for DME in the absence of vitreomacular traction and laser; anti-VEGFs or steroids should be considered as the treatment of choice.

Control of systemic risk factors

Strict glycemic and blood pressure control remains the hallmark of prevention and progression of DME. It is also important to assess the renal status and refer to a physician for adequate control.^[22] Glitazones and underlying hematological disorders,

such as idiopathic thrombocytopenic purpura or multiple myeloma, can also result in persistent DME. Reevaluation of the systemic status especially hypertension, anemia, and renal status in patients with bilateral neurosensory detachments at the fovea unresponsive to treatment is recommended. A rapidly progressing DR or a bilateral central retinal vein occlusion may be due to blood dyscrasias, and a complete hemogram with peripheral blood smear is also recommended. Epidemiological studies define asymmetric DR as none/mild DR in one eye and severe PDR in the other, a difference of two steps in the two eyes persisting for at least 2 years. In these clinical situations, carotid Doppler must be performed. An underlying systemic cause such as carotid artery/ophthalmic artery stenosis should be considered.

Management of DME in patients with other associated ocular problems

Proliferative diabetic retinopathy (PDR) with DME

Both PDR and DME are distinct patterns of retinal microvascular features that reflect small-vessel disease. Among patients with T2DM, the presence of DME in PDR can be associated with an increased risk of incident cardiovascular disease.^[37]

Treatment naïve PDR should be treated with pan-retinal photocoagulation (PRP). In the presence of extra macular traction, PRP should be done 2DD away from the traction and DME treated as per standard protocol. In the presence of vision-threatening traction, vitrectomy is indicated in addition to PRP. The presence of traction, threatening, or involving fovea is an indication for surgery. One must assess the extent of traction and vascularity of the proliferation as anti-VEGFs in such situations should be avoided as it can lead to worsening of traction or Crunch syndrome^[4]

In presence of a vitreous hemorrhage, where the view of the retina is compromised, a B Scan should be done to rule out traction at the macula. In presence of traction, a vitrectomy is indicated. In absence of traction, PRP should be done to the extent and area possible. Anti-VEGFs can be used to treat DME and may prevent re-bleed from neovascularization elsewhere in the eye. Nonresolving vitreous hemorrhage requires vitrectomy.

The renal status should be evaluated in eyes with sudden onset of bullous or exudative retinal detachment post PRP.

DME in pseudophakic eyes

Macular edema (ME) may be secondary to many retinal diseases.^[4,38] Therefore, before treatment is initiated, it is necessary to differentiate DME from pseudophakic cystoid macular edema (PCME)/Irvin–Gass syndrome. By performing an OCT before cataract surgery in eyes with suspected DME, one can anticipate DME or progression of DME following surgery. On FFA, pseudophakic edema will show a diffuse petaloid type of leakage with disc leakage, with the absence of microaneurysms and hard exudates around the edema.^[4] The presence of hard exudates, microaneurysms, or DR in the other eye strongly favor DME.^[38] In the presence of DME with no component of Irvine–Gass syndrome, treatment with anti-VEGFs can be initiated for CI-DME. First-line treatment with topical or subtenon's steroids is recommended for pseudophakic edema. In the presence of both DME and Irvine–Gass syndrome topical nonsteroidal

anti-inflammatory drugs (NSAIDs) should be used followed by anti-VEGFs.^[41] In nonresponders who have already been treated with anti-VEGFs (after 3–6 injections), it is reasonable to switch to steroids.^[39,40]

DME during pregnancy

With the increase in the prevalence of T2DM in the younger age group and increasing gestational age worldwide, there is a proportional increase in the number of pregnant women with diabetes.^[41] The prevalence of DR in early pregnancy in T2DM is estimated at 14%.^[42] While gestational diabetes is not associated with an increased risk of developing DR, those with undiagnosed T2DM may present with DR during or after pregnancy.

All pregnant women should be screened for DR every trimester during pregnancy. If DR has progressed in the third trimester, monitoring should be continued in the postnatal period up to 12 months. Communication and close collaboration between obstetricians and ophthalmologists is mandatory. Counseling regarding the effect of pregnancy on DR should ideally be initiated before pregnancy. Very little is known regarding the management of DME in pregnancy.^[43] DME has been reported to spontaneously regress post-partum.^[4,41] Therefore, a period of close observation may be reasonable. However, if there is a progressive deterioration of vision, the use of intravitreal steroids, particularly dexamethasone implants, is recommended. However, the patients should be fully informed about the possibility of cataract associated with the use of steroid implants. PDR in pregnant women must always be treated, given the risk of progression and the difficulties faced with multiple visits. Treatment should ideally be started before the onset of pregnancy, especially for severe NPDR and PDR,^[44] and therefore stabilized prior to conception.

The use of IVI anti-VEGFs in pregnancy is not recommended because of potential effects on developing embryos or fetus. It is therefore recommended that women should wait at least 3 months after the last intravitreal injection before conceiving.^[45,46]

DME in type I diabetes

Although DME is considered to be more prevalent in T2DM, the Diabetes Control and Complications Trial (DCCT) reported that 27% of the individuals with type 1 diabetes (T1DM) developed DME within 9 years of onset of diabetes.^[47] The annual incidence of DME in T1DM ranged from 0.9% to 2.3% and from 1.25% to 1.40% in T2DM.^[48] The prevalence of DME in T1DM was shown to be between 4.2% and 7.9% in population-based studies.^[49]

Data from the 25-year follow-up of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) showed that in the T1DM cohort, almost all patients (97%) developed DR over time, with a third to a half going on to develop vision-threatening disease (42% developed PDR, 29% developed DME, and 17% developed CSME).^[50] The 14-year incidence of DME in T1DM was shown to be 26%.^[19]

Management of DME in T1DM is similar to that in T2DM; however, they need more frequent and regular monitoring by the diabetologist/endocrinologist for glycemic control. Puberty is a well-known risk factor for DR in T1DM, and DR and DME

can progress rapidly during pregnancy especially in T1DM (see the section on pregnancy).^[51] Data from the DCCT showed that severity of retinopathy was associated with increased triglycerides and inversely associated with high-density lipoprotein (HDL) in T1DM. Higher serum lipids have also been shown to be associated with an increased risk of CSME and retinal hard exudates in T1DM.^[52]

Diabetic ketoacidosis (DKA) in T1DM may present with bilateral DME aggravated by fluid overload that resolves without any active ocular intervention.^[53] Therefore, systemic evaluation is very important in those with T1DM presenting with DME. Reports on the management of DR in young people with diabetes are limited given that clinical trials for DR subjects are over the age of 18 years. However, disease progression is no different between young and adult-onset diabetes, and treatment indications are similar to T2DM.^[41] The use of IVI of anti-VEGFs in children is limited and most reports are on the management of retinopathy of prematurity. Anti-VEGFs are well tolerated in this group; however, compliance is more challenging than in adults, and extra efforts should be made to counsel these patients.^[54]

DME in vitrectomized eyes

Eyes with macular edema after vitrectomy are likely to have poorer initial VA, thinner central macular thickness, greater prevalence of PDR, prior treatments as laser photocoagulation or other treatments for DME, prior cataract surgery, and longer duration of diabetes.^[55] Considering these factors, treatment for DME in a vitrectomized eye is challenging. Studies suggest secretion of type II procollagen and a lack of high molecular weight hyaluronan following pars plana vitrectomy.^[56] The pharmacokinetic parameters of IVI of anti-VEGFs may hence be affected as the ambience of the vitreous cavity is altered.^[57] There is limited data available based on a preferred agent for the treatment in these eyes.

A recent report comparing the effectiveness of ranibizumab injections for the treatment of DME in eyes with and without previous vitrectomy over 2 years showed similar outcomes.^[58] Koyanagi *et al.*^[59] also conducted a similar study and reported no significant differences in the mean changes of BCVA and central macular thickness between both groups at 6 months. However, some reports show a reduced efficacy of IVI anti-VEGFs in vitrectomized eyes.^[60]

Intravitreal steroids are effective in these eyes. Intravitreal dexamethasone implant has also been shown to have similar efficacy in both vitrectomized and nonvitrectomized eyes. In pseudophakic eyes with CI-DMI, intravitreal steroids can be considered as the first choice in suitable cases.^[57] Fluocinolone implant (Ileuvin) has also been shown to be effective in vitrectomized eyes.^[61]

Based on current evidence, both anti-VEGFs and steroids have their role in the treatment of DME in vitrectomized eyes.

DME in the presence of macular ischemia

Ischemic maculopathy may also explain poor vision despite adequate treatment for associated DME.^[4,62,63] An enlarged foveal avascular zone (FAZ) or irregular margin of FAZ on FFA are well-defined signs of macular ischemia. However, the best parameter to assess macular ischemia on OCT-A is unclear.^[4,63] Macular laser photocoagulation should be avoided in eyes

with diabetic macular ischemia. These eyes should be treated with anti-VEGFs or steroids for the associated DME. There is insufficient evidence of any adverse effects of these treatments on FAZ parameters.

DME in glaucomatous eyes

The management of DME in eyes with established glaucoma or those being treated for ocular hypertension or steroid responders should preferably be carried out with either macular laser or anti-VEGFs. Intraocular pressure (IOP) should be monitored regularly after each intravitreal injection and preoperative IOP-lowering agents should be used to prevent spikes in pressure. The use of steroids should be avoided in these patients. If necessary, augmentation of anti-glaucoma medications may be needed.^[4]

DME with cataract

Visually disabling cataract can coexist with DME. Where possible, DME should be stabilized before cataract surgery. Patients should be counseled on the visual outcome following cataract surgery as the vision may not be as good as those without DR. In some cases, complete resolution of DME may not be achieved, and it is advisable to progress with concurrent or post-cataract surgery IVI anti-VEGFs or steroid therapy. In the presence of clinically significant cataracts with poor view of the fundus and preexisting DME, surgery can be planned along with IVI anti-VEGFs or steroids. Treatment can also be planned 2 weeks after surgery and subsequent protocol continued. Postoperative topical NSAIDs are also recommended to prevent pseudophakic macular edema.^[4,41,64]

NdYAG laser capsulotomy may also be required during the course of therapy for DME and no extra precautions need be taken. However, visual prognosis must be explained.

DME with optic nerve abnormalities

Optic nerve abnormalities may rarely complicate the clinical picture of DME. DME can coexist with diabetic papillopathy or anterior ischemic optic neuropathy (AION). Diabetic papillopathy is usually not associated with visual field defects and afferent pupillary defects; it has a milder visual loss and invariably resolves spontaneously with good diabetic control and results in negligible residual visual debilitation. Malignant hypertension-associated disc edema could be discerned with a blood pressure assessment. FFA plays an important role in differentiating AION from diabetic papillopathy with AION showing early disc hypofluorescence due to hypoperfusion with late leakage around the affected segment. In contrast, a very early disc leakage that increases with time is seen in diabetic papillopathy. FFA will also show other features of DR. Treatment should be based on the primary underlying cause.^[4]

DME with mixed retinopathy

Hypertension is one of the commonest comorbidities associated with diabetes, and hypertensive retinopathy can often coexist with DR and has inspired the term "mixed retinopathy." Elevated blood pressure is an independent risk factor for both development and subsequent progression of DR.^[65] Macular star exudates is a classic feature seen in hypertensive retinopathy. Malignant hypertension is evidenced by disc edema with peripapillary hemorrhages and edema.^[66] It is of paramount importance to differentiate

mixed retinopathy from other vascular diseases such as central retinal vein occlusion and ocular ischemic syndrome. Prompt control of hypertension should be advised by all ophthalmologists.

DME with lattice degenerations

Retinal detachment is a rare complication of intravitreal injections. The vitreous in diabetic patients undergo structural changes and enzymatic vitreolysis.^[67] Both IVI anti-VEGFs and increasing age are risk factors for posterior vitreous detachment.^[68] Therefore, careful examination of the periphery and prophylactic treatment of any lesions that could predispose to retinal detachment is advisable. The interval between laser prophylaxis and anti-VEGFs should ideally be 3 weeks.^[4]

Blepharitis and external eye infection

People with diabetes are more susceptible to any infection, including ocular infection. The presence of blepharitis was shown to be a significant risk factor for endophthalmitis following intravitreal injections.^[69] Therefore, it is recommended that any active external infection including blepharitis should be treated prior to anti-VEGF therapy. In addition, eyelid checks before the injection, avoidance of subconjunctival anesthesia, and administration of povidone-iodine and topical antibiotics immediately after intravitreal injection are important steps to avoid endophthalmitis.

Managing DME in patients with other systemic problems

DME and dyslipidemia

Increased levels of total cholesterol, triglycerides, and low-density lipoproteins, as well as low high-density lipoproteins, have been implicated in the pathogenesis of DME.^[70-72] These observations led to studies testing lipid-lowering drugs such as fenofibrate and simvastatin in reducing the severity of DME and progression of DR.^[73,74] The beneficial effects of fenofibrate on DR progression and incidence of treatable DME were observed in people with normal lipid levels, suggesting that the effects of fenofibrate may not be due to the lipid-lowering effects of the drug.^[75,76] Lipid-lowering therapy has also been shown to reduce the severity and foveal migration of hard exudates in DME.^[77] The beneficial role of lipid-lowering drugs in the management of DME and DR is emerging from real-world scenario studies.^[78]

DME and anemia

Anemia has been indicated as an independent factor for the early progression of diabetes-related complications^[79] and is considered to worsen DME.^[80] Studies have shown that hemoglobin levels of <12 g/dL result in doubling the risk of DR.^[81] The majority of patients with anemia have an underlying renal dysfunction, which affects the production of erythropoietin (EPO). EPO enhances the function of the blood-retinal barrier, increases oxygenation, and protects against the damaging effects of VEGF, and may also have a neuroprotective role in the retina.^[82] Treatment with subcutaneous EPO injections has been shown to improve DME.^[4,82] However, EPO may also have an aggravating role as it has been shown to be important in the angiogenic processes in DR, especially at the proliferative stage. Additionally, anti-VEGF injections may be required in presence of center-involving DME.^[4]

DME and renal disease

The association between DR and renal disease has been extensively studied, including the influence of nephropathy on treatment outcomes in DME. The hallmark of established diabetic nephropathy is persistent albuminuria (category A3, severely increased) with coexisting DR, with no evidence of alternative kidney disease.^[83,84]

In T1DM, a clinical diagnosis of diabetic kidney disease can be made when there is persistent moderate (A2) or severe (A3) albuminuria or a persistent reduction in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m², occurring at least 5 years after the onset of diabetes. DR will also be present in over 95% of cases. Albuminuria does not have to be present to make a diagnosis providing eGFR is persistently <60 mL/min/1.73 m².

Clinical clues to coexisting renal disease include ischemic maculopathy, massive exudation at the posterior pole, and extensive peripapillary cotton wool spots. OCT features that may suggest coexisting renal disease include neurosensory detachment with diffuse thickening and neurosensory detachment refractory to anti-VEGFs. However, larger studies are required to confirm these observations.

Other comorbidities that can exist with nephropathy can also influence DME. For example, hypertension (which may present as mixed retinopathy), and anemia (especially patients on EPO; EPO may improve DME but worsen NPDR/PDR), patients on or after dialysis (wherein reduction in neurosensory detachment and central subfield thickness due to improvement in uremia and volume overload may occur), post-renal transplant, risk of fingolimod-induced CME, combined renal-pancreatic transplant, or only pancreatic transplant can show signs of initial worsening followed by improvement.

Multiple recent studies have shown that systemic absorption of IVI anti-VEGFs may cause accelerated hypertension, worsening proteinuria, glomerular disease, thrombotic microangiopathy, and possible chronic renal function decline. However, it is also important to note that diabetes itself can cause nephropathy independently. These have to be monitored by a physician when the patients are treated for DME by an ophthalmologist.

DME with cardiovascular disease (CVD)

DME and DR are associated with increased risk of incident CVD, which includes coronary heart disease, stroke, or death from cardiovascular causes. Persons with DME or PDR were more likely to have incident CVD (IRR: 1.39; 95% CI: 1.16–1.67) and fatal CVD (IRR: 2.33; 95% CI: 1.49–3.67) compared with those without DME or PDR.^[30] Treatment with anti-VEGFs should not be initiated if a patient had a stroke (cerebrovascular accidents) or myocardial infarction within the previous 3 months; PRP or steroid treatments should be considered in these patients. However, if the event occurred more than 3 months previously treatment with anti-VEGFs can be initiated. However, if systemic risks of thromboembolic phenomenon are significant, it is best to consult a physician first.^[4]

DME in the presence of systemic infection

When individuals with diabetes develop an infection, it can be more difficult to treat due to fluctuations in blood glucose levels, the presence of other diabetic complications, and a

compromised immune system in people with uncontrolled diabetes. Diabetic nonhealing foot ulcer poses a risk of infection, and before treatment is started, it is important to ensure that the patient is being seen by a foot surgeon (podiatric surgeon) and a diabetologist. The patient's hands/attendant's hands must be clean/sterile before instilling eyedrops. The patient should be counseled to do proper foot dressing to avoid any eye infection post anti-VEGF treatment. If there is an active foot infection, anti-VEGF injections should be postponed and noninvasive alternatives such as focal laser photocoagulation should be done if possible.

DME with sleep apnea

Obstructive sleep apnea (OSA) is a sleep disorder characterized by episodes of shallow or paused breathing during sleep leading to hypoxemia, arousal, and sleep fragmentation, affecting 58% of normal individuals and 86% of patients with diabetes.^[85] The intermittent episodes of hypoxia during OSA accelerate damage to the retinal vasculature and play a role in the development of DR.^[86]

Chang *et al.*,^[85] in a retrospective, cross-sectional study of 317 patients, reported a positive correlation between severe OSA and DR. When compared to patients with mild-to-moderate OSA, patients with severe OSA were found to be at a two- to threefold increased likelihood of having DR, PDR, and DME.^[86] In another study, severe OSA with desaturation parameters (SPO₂) below 90% was shown to be a predictive factor for DME.^[87] Once OSA is detected, patients can undergo formal diagnostic polysomnography. Continuous positive airway pressure (CPAP), a treatment for OSA, has been shown to stop and reverse DR and DME progression.^[85]

DME in patients with hypertension

The presence of neurosensory detachment and retinal thinning on OCT and fluctuations in central retinal thickness indicate associated poor blood pressure control.^[88-91] Renal disease-associated hypertension and anemia need to be controlled prior to considering intravitreal anti-VEGFs.^[91] It is preferable to avoid anti-VEGF in uncontrolled hypertension. Risk of vascular events increases if blood pressure is $>180/110$ mm Hg. While the risk of vision loss is particularly high if anti-VEGF agents are avoided for too long, it is preferable to defer any intravitreal injection until control of blood pressure; in addition, patients and physicians should be advised on the urgency to initiate treatment for DME. In eyes with DME that respond favorably to anti-VEGF agents, controlling blood pressure can have a further beneficial effect and hence should be encouraged.

DME in patients with uncontrolled diabetes

Poor glycemic control is an independent marker for the progression of DR and DME. Strict glycemic control is useful at any stage of DR.^[4] Poor or fluctuating glycemic control can alter the compliance of regular monthly intravitreal injections. Other systemic comorbidities in people with diabetes, such as diabetic kidney disease, uncontrolled hypertension, and cardiovascular disease, can also affect the adherence to follow-ups following anti-VEGFs.

Areas requiring further research

DME in patients who underwent bariatric surgery

A meta-analysis showed the impact of bariatric surgery in reducing the progression of DR.^[92] Brynskov *et al.*^[93] reported a

clinically negligible but statistically significant foveal thickening 6 months following bariatric surgery. Further research is required to understand the impact of bariatric surgery on DME and whether sudden normalization or improvement of diabetes in patients with bariatric surgery will have a similar effect as conventional anti-diabetic therapy inducing a rapid decline in HbA1c levels. As such, all patients who undergo bariatric surgery require close observation of initial worsening symptoms followed by long-term improvement of DR.

Conclusion

DME is preventable to some extent, and there is a need to optimize the control of systemic factors, including hyperglycemia, hyperlipidemia, and blood pressure. Thus, the care should be done holistically by a multidisciplinary team with the physician or an endocrinologist, internal medicine specialist or primary care physician being the center of a patient's care.

There have been significant advances in the management of DME. However, DME management remains suboptimal in many patients with diabetes. The recommendations given in this article are based on expert evaluation, and current evidence and aim to help guide the optimal choice of treatment and regimen for DME in India. Though anti-VEGFs are the first line of management, coexisting ocular diseases and associated comorbidities may alter the management strategy.

Acknowledgements

This work was supported by the ORNATE India project funded by the GCRF UKRI (MR/P207881/1).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum?. *Indian J Endocrinol Metab* 2016;20:546-51.
- Ryan SJ, Sadda SR. *Ryan's Retinal Imaging and Diagnostics E-Book*. 6th ed. Elsevier Health Sciences; 2018.
- Midena E, Bini S. Multimodal retinal imaging of diabetic macular edema: Toward new paradigms of pathophysiology. *Graefes Arch Clin Exp Ophthalmol* 2016;254:1661-8.
- Raman R, Bhende M. Diabetic Macular Edema. *Sci J Med Vis Res Foun* 2015;XXXIII: 50-6.
- Midena E, Pilotto E, Bini S. Hyperreflective intraretinal foci as an OCT biomarker of retinal inflammation in diabetic macular edema. *Invest Ophthalmol Vis Sci* 2018;59:5366.
- Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol* 1985;103:1796-806.
- Marashi A. Non-central diabetic clinical significant macular edema treatment with 532nm sub threshold laser. *Adv Ophthalmol Vis Syst* 2018;8:151-4.
- Degirmenci MF, Demirel S, Batoglu F. Short-term efficacy of micropulse yellow laser in non-center-involving diabetic macular edema: Preliminary results. *Turk J Ophthalmol* 2018;48:245-9.
- Perente I, Alkin Z, Ozkaya A, Dardabounis D, Ogredren TA, Konstantinidis A. Focal laser photocoagulation in non-center involved diabetic macular edema. *Med Hypothesis Discov Innov Ophthalmol* 2014;3:9-16.
- Bougatsou P, Panagiotopoulou EK, Gkika M, Dardabounis D, Konstantinidis A, Sideroudi H. Comparison of subthreshold 532 nm diode micropulse laser with conventional laser photocoagulation in the treatment of non-centre involved clinically significant diabetic macular edema. *Acta Medica* 2020;63:25-30.
- Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117:1064-77.
- Aiello LP, Beck RW, Bressler NM, Browning DJ, Chalam KV, Davis M. Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. *Ophthalmology* 2011;118:e5-14.
- Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 2013;120:2013-22.
- Cheung N, Ming C, Cheung G. Management of diabetic macular oedema: New insights and global implications of DRCR protocol V. *Eye* 2019;34:999-1002.
- Cekiç O, Bardak Y, Tig̃ US. Quantitative evaluation of reduction of plaque-like hard exudates in diabetic macular edema after intravitreal triamcinolone injection. *Int Ophthalmol* 2008;28:95-9.
- Relhan N, Flynn HW. The early treatment diabetic retinopathy study historical review and relevance to today's management of diabetic macular edema. *Curr Opin Ophthalmol* 2017;28:205-12.
- Srinivas S, Verma A, Nittala MG, Alagorie AR, Nassisi M, Gasperini J. Effect of intravitreal ranibizumab on intraretinal hard exudates in eyes with diabetic macular edema. *Am J Ophthalmol* 2020;211:183-90.
- Shimura M, Kitano S, Muramatsu D, Fukushima H, Takamura Y, Matsumoto M. Real-world management of treatment-naïve diabetic macular oedema in Japan: Two-year visual outcomes with and without anti-VEGF therapy in the STREAT-DME study. *Br J Ophthalmol* 2020;104:1209-15.
- Wenick AS, Bressler NM. Diabetic macular edema: Current and emerging therapies. *Middle East Afr J Ophthalmol* 2012;19:4-12.
- Nguyen QD, Shah SM, Khwaja AA, Channa R, Hatef E, Do DV, et al. Two-year outcomes of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology* 2010;117:2146-51.
- Payne JF, Wykoff CC, Clark WL, Bruce BB, Boyer DS, Brown DM. Randomized trial of treat and extend ranibizumab with and without navigated laser versus monthly dosing for diabetic macular edema: TREX-DME 2-year outcomes. *Am J Ophthalmol* 2019;202:91-9.
- Karim R, Tang B. Use of antivascular endothelial growth factor for diabetic macular edema. *Clin Ophthalmol* 2010;4:493-517.
- Baker CW, Glassman AR, Beaulieu WT. Effect of initial management with aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: A randomized clinical trial. *JAMA* 2019;321:1880-94.
- Chhablani J, Shaikh A, Goud A. Asia-Pacific technology and trend survey 2016-2017. *Asia-Pac J Ophthalmol* 2019;8:43-54.
- Maturi RK, Glassman AR, Liu D, Beck RW, Bhavsar AR, Bressler NM, et al. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: A DRCR Network Phase 2 randomized clinical trial. *JAMA Ophthalmol* 2018;136:29-38.
- Regillo CD, Callanan DG, Do DV, Fine HF, Holekamp NM, Kuppermann BD. Use of corticosteroids in the treatment of patients

- with diabetic macular edema who have a suboptimal response to Anti-VEGF: Recommendations of an expert panel. *Ophthalmic Surg Lasers Imaging Retina* 2017;48:291-301.
27. Shin YU, Hong EH, Lim HW, Kang MH, Seong M, Cho H. Quantitative evaluation of hard exudates in diabetic macular edema after short-term intravitreal triamcinolone, dexamethasone implant or bevacizumab injections. *BMC Ophthalmol* 2017;17:182.
 28. Mukkamala L, Bhagat N, Zarbin MA. Practical lessons from protocol I for the management of diabetic macular edema. *Dev Ophthalmol* 2017;60:91-108.
 29. Mansour AM, El Jawhari K, Arevalo JF. Role of peripheral pan-retinal photocoagulation in diabetic macular edema treated with intravitreal aflibercept. *Clin Ophthalmol* 2019;13:695-700.
 30. Brown DM, Ou WC, Wong TP, Kim RY, Croft DE, Wykoff CC, *et al.* Targeted retinal photocoagulation for diabetic macular edema with peripheral retinal nonperfusion: Three-year randomized DAVE trial. *Ophthalmology* 2018;125:683-90.
 31. Bonnin S, Sandali O, Bonnel S. Vitrectomy with internal limiting membrane peeling for tractional and nontractional diabetic macular edema: Long-term results of a comparative study. *Retina* 2015;35:921-8.
 32. Kadonosono K, Itoh N, Ohno S. Perifoveal microcirculation before and after vitrectomy for diabetic cystoid macular edema. *Am J Ophthalmol* 2000;130:740-4.
 33. Christoforidis JB, D'Amico DJ. Surgical and other treatments of diabetic macular edema: An update. *Int Ophthalmol Clin* 2004;44:139-60.
 34. Modarres M. Vitrectomy for diabetic macular edema; where are we?. *J Curr Ophthalmol* 2016;28:161-2.
 35. Jackson TL, Nicod E, Angelis A, Grimaccia F, Pringle E, Kanavos P. Pars plana vitrectomy for diabetic macular edema: A systematic review, meta-analysis, and synthesis of safety literature. *Retina* 2017;37:886-95.
 36. Ichiyama Y, Sawada O, Mori T. The effectiveness of vitrectomy for diffuse diabetic macular edema may depend on its preoperative optical coherence tomography pattern. *Graefes Arch Clin Exp Ophthalmol* 2016;254:1545-51.
 37. Xie J, Ikram MK, Cotch MF, Klein B, Varma R, Shaw JE. Association of diabetic macular edema and proliferative diabetic retinopathy with cardiovascular disease: A systematic review and meta-analysis. *JAMA Ophthalmol* 2017;135:586-93.
 38. Munk MR, Jampol LM, Simader C, Huf W, Mittermüller TJ. Differentiation of diabetic macular edema from pseudophakic cystoid macular edema by spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci* October 2015;56:6724-33.
 39. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, *et al.* Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica* 2017;237:185-222.
 40. Maggio E, Mauro S, Polito A, Massimo G, Bauci F, Pertile G. Optical coherence tomography biomarkers in diabetic macular edema treated with anti-VEGF. *Invest Ophthalmol Vis Sci* 2018;59:4841.
 41. Amoaku WM, Ghanchi F, Bailey C, Banerjee S, Banerjee S, Downey L. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. *Eye* 2020;34:1-51.
 42. Rasmussen KL, Laugesen CS, Ringholm L, Vestgaard M, Damm P, Mathiesen ER. Progression of diabetic retinopathy during pregnancy in women with type 2 diabetes. *Diabetologia* 2010;53:1076-83.
 43. Morrison JL, Hodgson LA, Lim LL, Al-Qureshi S. Diabetic retinopathy in pregnancy: A review. *Clin Exp Ophthalmol* 2016;44:321-34.
 44. American Academy of Ophthalmology Retina/Vitreous Panel. 2019. Diabetic Retinopathy. Preferred Practice Pattern Guidelines.
 45. Australian Government, Department of Health, Therapeutic Goods Administration. Product Information for AusPAR: Lucentis, ranibizumab, Novartis Pharmaceuticals Australia, PM-2013-00985-1-5. 2014.
 46. Genentech I Highlights of Prescribing Information: Avastin (bevacizumab).
 47. White NH, Sun W, Cleary PA, Tamborlane WV, Danis RP, Hainsworth DP, *et al.* Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: Comparison of adults and adolescents. *Diabetes* 2010;59:1244-53.
 48. Romero-Aroca P, Fernández-Balart J, Baget-Bernaldiz M, Martínez-Salcedo I, Méndez-Marín I, Salvat-Serra M. Changes in the diabetic retinopathy epidemiology after 14 years in a population of Type 1 and 2 diabetic patients after the new diabetes mellitus diagnosis criteria and a more strict control of the patients. *J Diabetes Complications* 2009;23:229-38.
 49. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)* 2015;2:17.
 50. Klein R, Knudtson MD, Lee KE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: The twenty-five-year incidence of macular edema in persons with type 1 diabetes. *Ophthalmology* 2009;116:497-503.
 51. Vestgaard M, Ringholm L, Laugesen CS, Rasmussen KL, Damm P, Mathiesen ER. Pregnancy-induced sight-threatening diabetic retinopathy in women with Type 1 diabetes. *Diabet Med* 2010;27:431-5.
 52. Miljanovic B, Glynn RJ, Nathan DM, Manson JE, Schaumberg DA. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. *Diabetes* 2004;53:2883-92.
 53. Samanta R, Puthalath AS, Saraswat N, Agrawal A, Singh A, Mittal S. Rapidly reversing bilateral macular edema associated with fluid overload in a young type 1 diabetic. *Indian J Ophthalmol* 2019;67:1221-3.
 54. Lucentis® (ranibizumab solution for injection) [summary of product characteristics]. Dublin, Ireland: Novartis Europharm Ltd.; 2018.
 55. Bressler SB, Melia M, Glassman AR. Diabetic retinopathy clinical research network ranibizumab plus prompt or deferred laser for diabetic macular edema in eyes with vitrectomy before anti-vascular endothelial growth factor therapy. *Retina* 2015;35:2516-28.
 56. Itakura H, Kishi S, Kotajima N. Vitreous collagen metabolism before and after vitrectomy. *Graefes Arch Clin Exp Ophthalmol* 2005;243:994-8.
 57. Papastefanou VP, Dooley I, Zambakji H. Management of macular edema in vitrectomized patients with diabetes. *Expert Rev Ophthalmol* 2018;13:87-103.
 58. Gedar Totuk OM, Kanra AY, Bromand MN, Kilic Tezanlayan G, Ari Yaylali S, Turkmen I, *et al.* Effectiveness of intravitreal ranibizumab in nonvitrectomized and vitrectomized eyes with diabetic macular edema: A two-year retrospective analysis. *J Ophthalmol* 2020;2020. doi: 10.1155/2020/2561251.
 59. Koyanagi Y, Yoshida S, Kobayashi Y. Comparison of the effectiveness of intravitreal ranibizumab for diabetic macular edema in vitrectomized and nonvitrectomized eyes. *Ophthalmologica* 2016;236:67-73.
 60. Chen Y-Y, Chen P-Y, Chen F-T, Chen YJ, Wang JK. Comparison of efficacy of intravitreal ranibizumab between non-vitrectomized and vitrectomized eyes with diabetic macular edema. *Int Ophthalmol* 2018;38:293-9.
 61. Estebainha R, Goldhardt R, Falcão M. A new approach for diabetic macular edema treatment: Review of clinical practice results with 0.19 mg fluocinolone acetonide intravitreal implant including

- vitrectomized eyes. *Curr Ophthalmol Rep* 2020;8:1-10.
62. Marashi A. Management of diabetic macular edema: An algorithm for treatment decision-making. *Retinal Physician* 2016;13:50, 52-7.
 63. Pereira F, Godoy BR, Maia M, Regatieri CV. Microperimetry and OCT angiography evaluation of patients with ischemic diabetic macular edema treated with monthly intravitreal bevacizumab: A pilot study. *Int J Retina Vitreous* 2019;5:24.
 64. Furino C, Boscia F, Niro A, D'Addario M, Grassi MO, Saglimbene V. Diabetic macular edema and cataract surgery: Phacoemulsification combined with dexamethasone intravitreal implant compared with standard phacoemulsification. *Retina* 2021;41:1102.
 65. Wong TY, Mitchell P. The eye in hypertension. *Lancet* 2007;369:425-35.
 66. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med* 2004;351:2310-7.
 67. Pai A, El Shafei MM, Mohammed OA. Current concepts in intravitreal drug therapy for diabetic retinopathy. *Saudi J Ophthalmol* 2010;24:143-9.
 68. Geck U, Pustolla N, Baraki H. Posterior vitreous detachment following intravitreal drug injection. *Graefes Arch Clin Exp Ophthalmol* 2013;251:1691-5.
 69. Lyall DA, Tey A, Foot B. Post-intravitreal anti-VEGF endophthalmitis in the United Kingdom: Incidence, features, risk factors, and outcomes. *Eye* 2012;1517-26.
 70. Raman R, Rani PK, Kulothungan V. Influence of serum lipids on clinically significant versus nonclinically significant macular edema: SN-DREAMS Report number 13. *Ophthalmology* 2010;117:766-72.
 71. Das R, Kerr R, Chakravarthy U. Dyslipidemia and diabetic macular edema: A systematic review and meta-analysis. *Ophthalmology* 2015;122:1820-7.
 72. Barter PJ, Nicholls S, Rye KA. Antiinflammatory properties of HDL. *Circ Res* 2004;95:764-72.
 73. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): A randomised controlled trial. *Lancet* 2007;370:1687-97.
 74. Chew EY, Davis MD, Danis RP, Lovato JF, Perdue LH, Greven C, *et al.* The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology* 2014;121:2443-51.
 75. Kim J, Ahn JH, Kim JH. Fenofibrate regulates retinal endothelial cell survival through the AMPK signal transduction pathway. *Exp Eye Res* 2007;84:886-93.
 76. Malik J, Melenovsky V, Wichterle D, Haas T, Simek J, Ceska R. Both fenofibrate and atorvastatin improve vascular reactivity in combined hyperlipidaemia (fenofibrate versus atorvastatin trial--FAT). *Cardiovasc Res* 2001;52:290-8.
 77. Gupta A, Gupta V, Thapar S. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. *Am J Ophthalmol* 2004;137:675-82.
 78. Kawasaki R, Konta T, Nishida K. Lipid-lowering medication is associated with decreased risk of diabetic retinopathy and the need for treatment in patients with type 2 diabetes: A real-world observational analysis of a health claims database. *Diabetes Obes Metab* 2018;20:2351-60.
 79. Taderegew MM, Gebremariam T, Tareke AA. Anemia and its associated factors among type 2 diabetes mellitus patients attending Debre Berhan Referral Hospital, North-East Ethiopia: A cross-sectional study. *J Blood Med* 2020;11:47-58.
 80. Ajoy Mohan V. K, Nithyanandam S, Idiculla J. Microalbuminuria and low hemoglobin as risk factors for the occurrence and increasing severity of diabetic retinopathy. *Indian J Ophthalmol* 2011;59:207-10.
 81. Aiello L. P, Cahill M. T, Wong J. S. Systemic considerations in the management of diabetic retinopathy. *Am J Ophthalmol* 2001;132:760-76.
 82. Mathew C, Yunirakasiwi A, Sanjay S. Updates in the management of diabetic macular edema. *J Diabetes Res* 2015;2015:794036.
 83. Selby NM, Taal MW. An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. *Diabetes Obes Metab* 2020;22:3-15.
 84. Hanna RH, Barsoum M, Arman F. Nephrotoxicity induced by intravitreal vascular endothelial growth factor inhibitors: Emerging evidence. *Kidney Int* 2019;572-80.
 85. Chang AC, Fox TP, Wang S, Wu AY. Relationship between obstructive sleep apnea and the presence and severity of diabetic retinopathy. *Retina* 2018;38:2197-206.
 86. Kent BD, McNicholas WT, Ryan S. Insulin resistance, glucose intolerance and diabetes mellitus in obstructive sleep apnoea. *J Thorac Dis* 2015;7:1343-57.
 87. Vié AL, Kodjikian L, Agard E, Voirin N, El Chehab H, Denis P. Evaluation of obstructive sleep apnea syndrome as a risk factor for diabetic macular edema in patients with type II diabetes. *Retina* 2019;39:274-80.
 88. Kong M, Kwun Y, Sung J. Association between systemic hypertension and macular thickness measured by optical coherence tomography. *Invest Ophthalmol Vis Sci* 2015;56:2144-50.
 89. Dupas B, Feldman-Billard S, Bui Quoc E. Influence of pulse pressure and spontaneous variations of macular thickness in patients with diabetic macular oedema. *Acta Ophthalmol* 2014;92:e372-6.
 90. Berger V, Munk MR, Lersch F. Association of intravitreal injections with blood pressure increase: The following excitement and anxiety response under intravitreal injection study. *JAMA Ophthalmol* 2019;137:87-90.
 91. Shah AR, Van Horn AN, Verchinina L, Wichorek M, Su L, Markel D. Blood pressure is associated with receiving intravitreal anti-vascular endothelial growth factor treatment in patients with diabetes. *Ophthalmol Retina* 2019;3:410-6.
 92. Kim YJ, Kim BH, Choi BM. Bariatric surgery is associated with less progression of diabetic retinopathy: A systematic review and meta-analysis. *Surg Obes Relat Dis* 2017;13:352-60.
 93. Brynskov T, Laugesen CS, Svenningsen AL. Monitoring of diabetic retinopathy in relation to bariatric surgery: A prospective observational study. *Obes Surg* 2016;26:1279-86.