

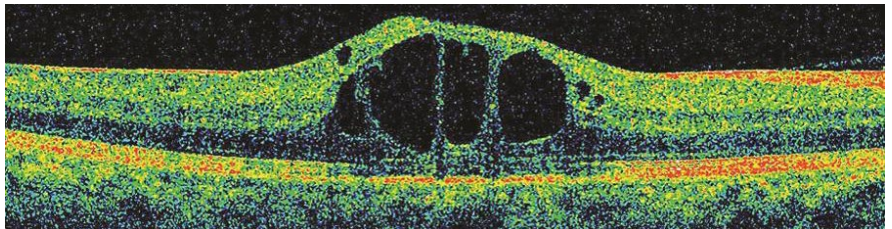
Diabetic Macular Edema: Diagnosis and Management

Diabetic retinopathy (DR) is the leading cause of new cases of blindness among adults aged 18 to 64 years in the United States.¹ Diabetic macular edema (DME), a severe complication of DR that occurs specifically as a result of inadequately treated diabetes mellitus (DM), has overtaken proliferative diabetic retinopathy as the most common cause of vision impairment in individuals with DM.² In recent epidemiologic studies, approximately 30% of patients worldwide with DM were found to have vision-threatening DR; and in the United States, 3.8% of patients were found to have DME.³

DME, which is characterized by hard exudates and edema within the macula secondary to damage to retinal microvasculature, is detected by clinical examination or with OCT. Before the advent of pharmacotherapy for DME, the first-line treatment was traditionally focal laser photocoagulation of the macula. More recently, large-scale clinical evidence from the DRCR.net has established intravitreal anti-VEGF injections as the first-line therapy, followed by the use of intravitreal corticosteroids if treatment response is unsatisfactory.⁴

Etiology and Pathogenesis

DR. DR develops from the loss of both endothelial tight junctions and pericytes in retinal capillaries, eventually leading to leakage of protein, lipids,



CENTRAL DME. Spectral-domain macular OCT shows central DME with intraretinal cystic spaces and disruption of central retinal architecture.

inflammatory molecules, and other plasma components into the interstitial space. Further production of proinflammatory cytokines and VEGF by retinal pigment epithelium, glial cells, and macrophages leads to breakdown of the blood-retina barrier, causing further leakage of fluid into the retina.

DME. DME arises from the accumulation of fluid, protein, and lipids throughout the layers of the retina in the form of intraretinal cystic spaces, best seen by OCT.⁵ It is now believed that the etiology of DME, though complex, is largely twofold.

First, retinal microvascular obstruction and capillary dropout throughout the retina in patients with poorly controlled DM lead to retinal ischemia. The subsequent hypoxia-induced upregulation of VEGF then causes neovascularization both in the retinal periphery and in existing macular vessels, increasing vascular permeability.

Second, in many patients with long-standing DM, production of free radicals and accumulation of

advanced glycosylation end products cause upregulation of proinflammatory cytokines such as interleukin (IL)-1 β and IL-6. This process leads to further vision-threatening consequences of DME as inflammation develops and vascular pericytes are lost. Compromised junctional proteins in macular microcapillaries cause them to become more liable to leakage, contributing to the extravascular fluid and hard lipid exudates that are a hallmark of DME.⁶

Diagnosis and Screening

Because of the insidious nature of both DR and DME, all diabetic patients should have an ophthalmic evaluation to screen for eye disease, consisting of a comprehensive eye examination, with ancillary testing and imaging as appropriate. According to the Academy's *Preferred Practice Patterns* guidelines for DR, patients with type 1 DM should be screened for DR starting five years after diagnosis of DM, while patients with type 2 DM should be screened for DR upon diagnosis and then annually or more often, depending on the severity of their systemic disease.⁷

Imaging. OCT has become a mainstay in screening and diagnosis. This

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Table 1: Important Recent Studies in DME Treatment

STUDY	GROUPS	CONCLUSIONS
Protocol I	<ul style="list-style-type: none"> • Sham + laser • Ranibizumab + laser • Ranibizumab + deferred laser • Corticosteroid + laser 	Both groups that received ranibizumab showed greater improvement (independent of when laser photocoagulation was performed) than other groups.
RISE/RIDE	<ul style="list-style-type: none"> • Sham injections • 0.3-mg ranibizumab • 0.5-mg ranibizumab 	Both dosages of ranibizumab improved VA compared with sham injections.
VISTA/VIVID	<ul style="list-style-type: none"> • Intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4) • IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8) • Macular laser photocoagulation 	Both IAI groups had similarly effective improvement in BCVA, significantly superior to those in the laser photocoagulation group.
Protocol T	<ul style="list-style-type: none"> • Ranibizumab • Bevacizumab • Aflibercept 	All three anti-VEGF agents are effective when VA loss is mild. In more severe cases, aflibercept is significantly more effective than the other two in improving VA and reducing central retinal thickness on OCT.
Protocol V	<ul style="list-style-type: none"> • Observation • Laser photocoagulation • Aflibercept 	No significant difference was seen between patients who were initially managed with aflibercept and those who were given aflibercept only when VA worsened from baseline by 10 letters.
Protocol U	<ul style="list-style-type: none"> • Ranibizumab + sham • Ranibizumab + dexamethasone implant 	Simultaneous administration of corticosteroids with ranibizumab decreased retinal thickness on OCT at six months, but the addition of steroid did not yield better VA results than ranibizumab alone.
MEAD	<ul style="list-style-type: none"> • Dexamethasone 0.35 mg • Dexamethasone 0.7 mg • Sham procedure 	Improved BCVA in the dexamethasone groups was significantly greater than sham.

modality allows clinicians to detect thickening, structural changes, and edema that are difficult to capture in a clinical funduscopy exam.

Nonmydriatic or mydriatic digital retinal photography is often used in comprehensive ophthalmology settings for noninvasive screening. It has the potential to be employed in combination with advanced artificial intelligence algorithms that automate the diagnostic process.^{8,9}

Classification. After DME has been detected, the ophthalmologist should perform a detailed clinical examination to determine its severity. DME is typically classified in the following three categories:

- **Mild:** Retinal thickening and hard exudates are present in the posterior pole but fall more than 1,000 µm outside the central macular subfield.
- **Moderate:** Retinal thickening or

hard exudates are present within the central subfield of the macula but do not involve the center.

- **Severe:** Retinal thickening or hard exudates involve the center of the macula.¹⁰

Treatment and Prevention

Treatment of DME begins with management of the systemic disease. Stringent regulation and treatment of hyperglycemia, hypertension, and hyperlipidemia can delay the onset and progression of various microvasculopathies, including DR and DME.

Treatment options for DME vary depending on the severity of disease and the patient’s baseline visual acuity (VA). However, on the basis of recent studies by the DRCR.net, discussed below, ophthalmologists have generally adopted anti-VEGF intravitreal therapy as the first-line treatment. (See Table 1

for an overview of important treatment studies.)

Laser. Laser photocoagulation became the primary therapy for DME in the mid-1980s, when the Early Treatment Diabetic Retinopathy Study demonstrated its ability to decrease the risk of vision loss. However, the introduction of anti-VEGF drugs in the 2000s changed the treatment paradigms because these drugs can reverse vision loss, an outcome that is uncommon with laser therapy.¹¹ The DRCR.net Protocol I study showed a significant improvement in participants treated with ranibizumab and laser therapy (whether on a fixed or flexible schedule) compared with those treated with sham injections and laser therapy.

Anti-VEGF agents. The RISE and RIDE studies, performed in 2010, looked at three groups of patients with a baseline VA of 20/30 or worse: The

treatment groups received either 0.3-mg or 0.5-mg doses of ranibizumab, and a control group received sham injections. Both treatment groups experienced greater improvement in BCVA than did the control group.¹²

Similarly, in the VISTA and VIVID studies of patients with central DME, 2 mg of intravitreal aflibercept, administered either every four or eight weeks (the latter after five monthly doses), produced visual gains that were far superior to the results with laser therapy.¹³

The DRCR.net Protocol T study compared the efficacy of the three anti-VEGF drugs currently in widespread clinical use for DME: ranibizumab, aflibercept, and bevacizumab (used off label). Participants were randomly assigned to one of the three treatment groups. The study concluded that aflibercept is the most effective drug in eyes with a baseline VA of 20/50 or worse. There was no significant difference in efficacy among the drugs in eyes with better baseline VA.

In the DRCR.net Protocol V study, the investigators compared aflibercept, laser photocoagulation, and observation in the initial management of patients with center-involving DME and a baseline BCVA of 20/25 or better. No significant difference was found, suggesting that in eyes with mild VA loss, the three approaches are equally effective.¹⁴

Corticosteroids. In approximately 40% of patients with chronic DME, anti-VEGF therapy is unsuccessful or inadequate. Intravitreal corticosteroid therapy is indicated for these patients,

as it is presumed that inflammation may be contributing to the pathogenesis of DME. Treatment can be administered via intravitreal injection or sustained-release intravitreal implants. Physicians considering intravitreal steroids should keep in mind the risks, including premature cataract formation, increased IOP, and worsening vision loss.

As a second-line pharmacologic agent for DME, intravitreal corticosteroid implants have been associated with variable outcomes. For example, in the DRCR.net Protocol U study, patients with persistent DME who received intravitreal dexamethasone implants in combination with ranibizumab had decreased retinal thickening on OCT, although BCVA did not improve.

In the MEAD study of a dexamethasone implant, patients who completed the trial had a 0.9 letter gain in BCVA compared with those who dropped out. Among the participants, 37.5% had no change in BCVA, while 23.2% gained more than 10 letters, and 16.0% lost more than 10 letters.¹⁵

Putting it together. These data suggest a stepwise approach to treatment (see Table 2), with anti-VEGF treatment initiated in patients with moderate to severe DME (VA of 20/30 or worse). Approximately three months or more after starting anti-VEGF treatment, the patient should be reevaluated clinically and with OCT, and further treatment options should be considered if VA and/or central macular thickness have not improved or stabilized suffi-

ciently. If the response to anti-VEGF therapy is suboptimal at this point, some retina specialists choose to initiate intravitreal corticosteroid therapy and focal or grid laser photocoagulation, while many others prefer to continue with six months of anti-VEGF injections before considering intravitreal corticosteroid therapy.

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See disclosure key, page 10. For full disclosures, see this article at aao.org/eyenet.

Table 2: Stepwise Approach to DME Treatment

Is central involvement detected on OCT?

- I. **If no**, recommend tight glycemic control and observe.
- II. **If yes**, evaluate the patient's visual acuity.
 - A. If VA is better than 20/30, observe or begin treatment with anti-VEGF drugs or focal or grid laser photocoagulation.
 - B. If VA is 20/30 to 20/40, begin anti-VEGF therapy with any of the three agents (aflibercept, bevacizumab, ranibizumab).
 - C. If VA is 20/50 or worse, begin anti-VEGF therapy with aflibercept.
 1. If anti-VEGF treatment fails or response is suboptimal, consider switching to a different anti-VEGF agent.
 2. After 24 weeks of anti-VEGF failure or suboptimal response, consider intravitreal corticosteroid or focal or grid laser photocoagulation.