# MODULE 8.1
## Diabetic Macular Edema Classifications

Diabetic retinopathy (DR) and diabetic macular edema (DME) classifications include proliferative (PDR) and nonproliferative (NPDR) types of DR, vasogenic and nonvasogenic DME, tractional DME, mixed DME, focal and diffuse DME, and clinically significant macular edema (CSME).

**PDR and NPDR**

Retinal neovascularization is indicative of DR progression from nonproliferative to the more severe, proliferative form. PDR is defined by neovascularization at the optic disc (NVD) or elsewhere (NVE), preretinal hemorrhage, or vitreous hemorrhage; high-risk characteristics are mild NVD with vitreous hemorrhage, moderate-to-severe NVD with or without vitreous hemorrhage, and moderate NVE with vitreous hemorrhage. Patients can experience sudden visual loss with fibrovascular proliferation due to vitreous hemorrhage arising from new blood vessels or tractional retinal detachment resulting from progressive fibrosis.

**Proposed DME classifications**

DME is a sight-threatening complication of DR that is characterized by thickening of the central macula and surrounding noncentral macula.[1] Retinal edema is defined as any increase of fluid in retinal tissue that results in an increase in its volume.[2] This increase may initially be intracellular (eg, there is cytotoxic edema), but it can progress to an extracellular (vasogenic) form. DME can be broadly defined as retinal thickening within 2 disc diameters of the foveal center.[3] Vasogenic edema is directly associated with an alteration of the blood-retinal barrier (BRB). DME is associated with a high proportion of blindness among those with DR.[4] The severity grading scale for DME from the International Council of Ophthalmology is shown in the table below.

**Focal and Diffuse DME**

DME is often classified as focal or diffuse depending on the distribution of the fluid. These definitions are often controversial because there are different opinions about what is considered focal or diffuse distribution of the fluid. It is generally accepted that focal edema is usually the result of fluid leakage in a circumscribed area of the retina. This leakage originates from microaneurysms (MAs) that create a circular area of hard exudates, over time, around the area of edema. Focal DME has been associated with less macular thickening, better visual acuity, and less severe retinopathy severity than the diffuse form of the disease.[6] Diffuse edema represents more extensive breakdown of the BRB with leakage from both MAs and retinal capillaries.

## Table 1: International Classification of Diabetic Macular Edema

From the ICO Guidelines for Diabetic Eye Care February 2014[5]

| Diabetic Macular Edema | Defining Features |
|---|---|
| DME absent | No retinal thickening or hard exudates in posterior pole |
| DME present | Retinal thickening or hard exudates in posterior pole (Hard exudates are a sign of current or previous macular edema). |
| Mild DME | Retinal thickening or hard exudates in posterior pole but outside the central subfield of the macula (diameter 1000 µm) |
| Moderate DME | Retinal thickening or hard exudates within the central subfield of the macula but not involving the center point |
| Moderate DME | Retinal thickening or hard exudates involving the center of the macula |

Several definitions for focal and diffuse DME have been proposed based on 4 examination techniques used either singly or in combination[7]:

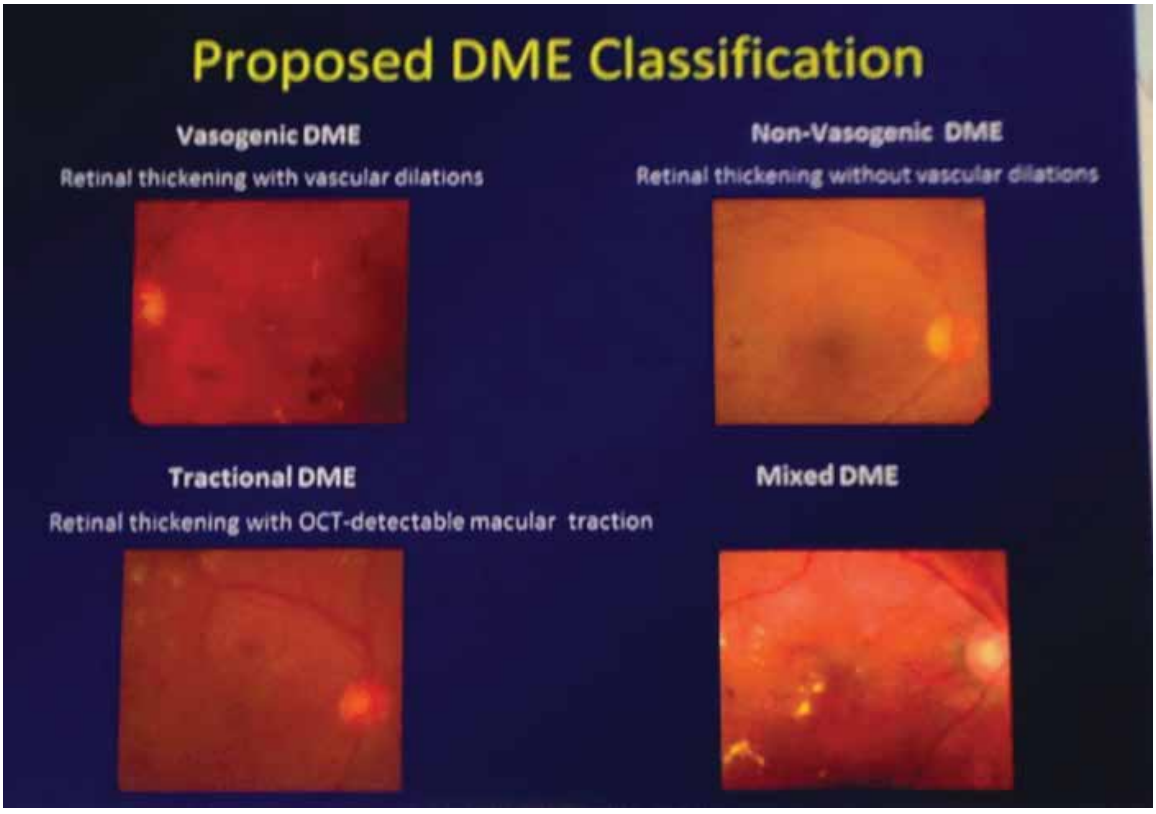
1. Fundus biomicroscopy
2. Color fundus photography
   - Diffuse and focal DME defined using this technique often use area criteria:
     - Diffuse DME: ≥2 disk areas of retinal thickening and involvement of the center of the macula[8]
     - Focal DME: <2 disk areas of retinal thickening, without involvement of the center of the macula[8]
   - The area definitions and involvement of the macular center for diffuse DME are not uniform
3. Fluorescein angiography (FA)
   - Several groups have classified DME as focal or diffuse based on FA characteristics[6,9-11]
   - Although fluorescein leakage was not included as part of the DME definition in the Early Treat ment Diabetic Retinopathy Study (ETDRS), FA was used to grade the proportion of leakage to classify edema as focal or diffuse[9]:
     - Diffuse DME: <33% of leakage associated with MAs
     - Intermediate DME: 33%-66% of leakage associated with MAs
     - Focal DME: ≥67% of leakage associated with MAs
4. Optical coherence tomography (OCT)
   - OCT has been used to define focal and diffuse DME using regional maps and cross-sectional scans[7]
     - For example, diffuse DME is associated with increasing numbers of elevated subfields[12]
     - Morphologic analyses of cross-sectional scans were used to define diffuse DME as thickened areas of lower reflectivity without cystoid spaces in the outer retina[13]

The correlation between OCT and FA findings in the course of CSME is high; about 60% of patients with foveal thickening and homogeneous intraretinal optical reflectivity on OCT have focal leakage on FA, whereas more than 90% of patients with diffuse cystoid leakage exhibit foveal thickening with decreased optical reflectivity in the outer retinal layers or foveal thickening with subretinal fluid accumulation on OCT.[6]

**CSME**

CSME is a form of DME that was precisely defined by the ETDRS.[3] Classification is based on the presence of retinal thickening or hard exudates within prespecified areas.[14] According to this definition, CSME is present if any of the following criteria is met:

- Any retinal thickening within 500 µm of the foveal center
- Hard exudates within 500 µm of the foveal center that are associated with adjacent retinal thickening (which may lie more than 500 µm from the foveal center)
- An area of retinal thickening at least 1 disc area in size, any part of which is located within 1 disc area of the foveal center



The "SAVE" grading protocol for CSME is based on OCT and FA,[16] defining 4 categories:

1. Subretinal fluid (category "S")
2. The planimetrically measured edematous area (category "A")
3. Vitreoretinal interface abnormalities (category "V")
4. CSME aetiology (category "E") defining the leakage source

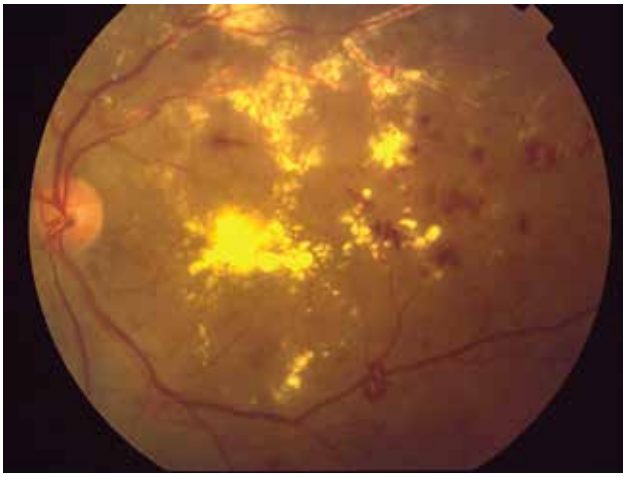
Atrophic, a new type of CSME, was described using the SAVE protocol. The SAVE protocol allows clinicians to define and further categorize clinical disease characteristics to design tailored therapeutic strategies.

# Focal/Diffuse DME

Focal edema

Focal edema is often associated with circinate rings of hard exudates (lipoprotein deposits) resulting from leakage of microaneurysms, which result of leakage of fluid in a circumscribed area of the retina. In this image, a clear circinate ring is visible superotemporal to the fovea, within the area of 2 disc diameters.

Diffuse edema



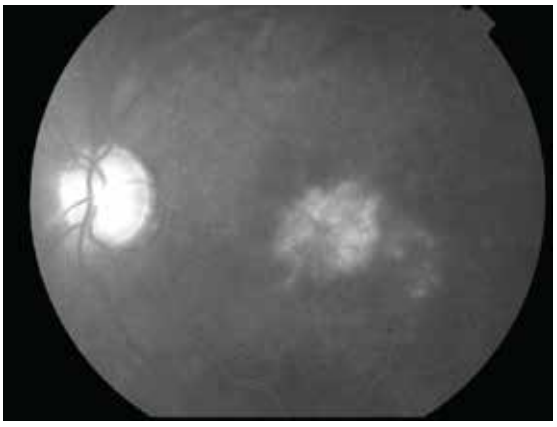
Diffuse edema represents more extensive breakdown of the blood-retinal barrier, with leakage from both microaneurysms and retinal capillaries. In this case, leakage arises from several points and no specific area can be determined as responsible for the leakage. Hard exudates do not take any particular configuration and span most of the posterior pole.

Diabetic Macular Edema: What is Focal and What is Diffuse? David J. Browning, Michael M. Altaweel, Neil M. Bressler, Susan B. Bressler, Ingrid U. ScottAm J Ophthalmol. Author manuscript; available in PMC 2009 November 30

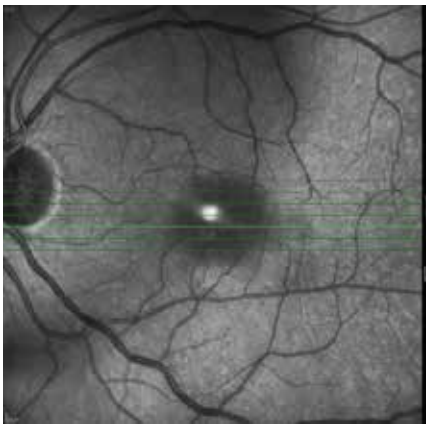
Diabetic macular edema (DME): overview of etiology, diagnosis, and treatment options, Patricio G. Schlottmann, M.D.

# OCT/FA correlation

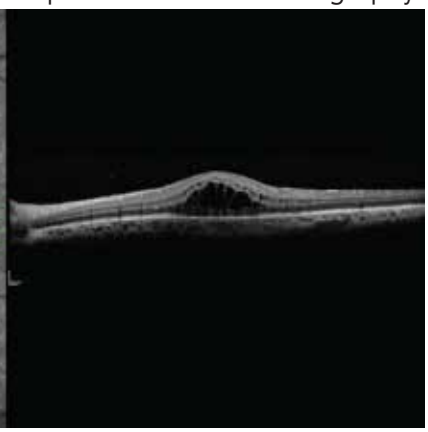
Fluorescein angiography



Infra red image



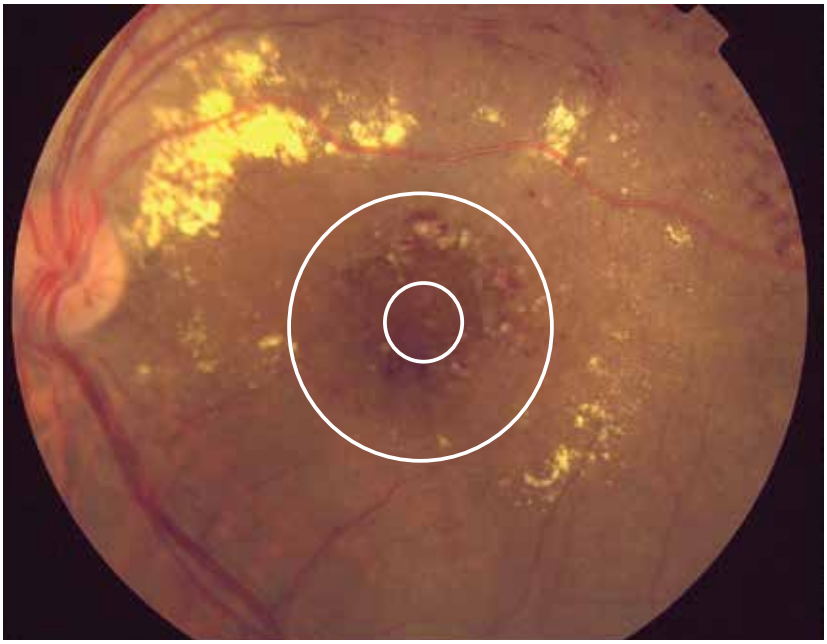
Optical coherence tomography



Correlation between OCT and fluorescein angiography findings in the course of CSME is fairly good: about 60% of patients with foveal thickening and homogeneous intraretinal optical reflectivity on OCT have focal leakage on fluorescein angiography, while more than 90% of patients with diffuse cystoid leakage exhibit foveal thickening with decreased optical reflectivity in the outer retinal layers or foveal thickening with subretinal fluid accumulation on OCT.

(Kang et al., 2004)

# Clinically Significant DME



Clinically significant macular edema (CSME) is a form of DME that was precisely defined by the Early Treatment Diabetic Retinopathy Study (ETDRS). Classification is based on presence of retinal thickening or hard exudates within pre specified areas.

Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report no 1. Arch Ophthalmol. 1985;103:1796-1806.

## References

1. Mitchell P, Wong TY for the Diabetic Macular Edema Treatment Guideline Working Group. Management paradigms for diabetic macular edema. *Am J Ophthalmol*. 2014;157:505-513.e1-8.

2. Cunha-Vaz J. Diabetic macular edema. *Eur J Ophthalmol*. 1998;8:127-130.

3. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report no. 1. Early Treatment Diabetic Retinopathy Study Research Group. *Arch Ophthalmol.* 1985;103:1796-1806.

4. Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. *Ophthalmology.* 1998;105:998-1003.

5. Internation Council of Ophthalmology. *ICO Guidelines for Diabetic Eye Care.* February 2014. http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf. Accessed October 21, 2015.

6. Kang SW, Park CY, Ham DI. The correlation between fluorescein angiographic and optical coherence tomographic features in clinically significant diabetic macular edema. *Am J Ophthalmol.* 2004;137:313-322.

7.Br owning DJ, Altaweel MM, Bressler NM, Bressler SB, Scott IU. Diabetic Retinopathy Clinical Research Network. Diabetic macular edema: what is focal and what is diffuse? *Am J Ophthalmol*. 2008;146:649-655, 655.1-6.

8. Laursen ML, Moeller F, Sander B, Sjoelie AK. Subthreshold micropulse diode laser treatment in diabetic macular oedema. *Br J Ophthalmol*. 2004;88:1173-1179.

9. Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Early Treatment Diabetic Retinopathy Study Research Group. *Arch Ophthalmol.* 1995;113:1144-1155.

10. McDonald HR, Schatz H. Grid photocoagulation for diffuse macular edema. *Retina.* 1985;5:65-72.

11. Kumar A, Sinha S, Azad R, Sharma YR, Vohra R. Comparative evaluation of vitrectomy and dye-enhanced ILM peel with grid laser in diffuse diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol.* 2007;245:360-368.

12. Browning DJ, Fraser CM. Regional patterns of sight-threatening diabetic macular edema. *Am J Ophthalmol.* 2005;140:117-124.

13. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. *Am J Ophthalmol.* 2006;142:405-412.

14. Cunha-Vaz J. Phenotypes and biomarkers of diabetic retinopathy. Personalized medicine for diabetic retinopathy: the Weisenfeld award. *Invest Ophthalmol Vis Sci*. 2014;55:5412-5419.

15. Cunha-Vaz J, Ribeiro L, Lobo C. Phenotypes and biomarkers of diabetic retinopathy. *Prog Retin Eye Res.* 2014;41:90-111.

16. Bolz M, Lammer J, Deak G, et al. SAVE: a grading protocol for clinically significant diabetic macular oedema based on optical coherence tomography and fluorescein angiography. *Br J Ophthalmol.* 2014;98:1612-1617.