MODULE 8.2
Diabetic Retinopathy Severity Scales

Diabetic retinopathy (DR) refers to the presence of the atypical retinal microvasculature seen in people with diabetes mellitus. The National Eye Institute projects that 7.2 million adults in the United States, aged 40 years and above, will suffer from DR by the year 2020.[1] The disease is classified into 2 types: nonproliferative (NPDR) and proliferative (PDR).[2] In general, direct ophthalmoscopy allows for an adequate assessment of DR presence. However, slit-lamp biomicroscopy with a condensing lens can enhance the evaluation of the disease. Diabetic macular edema (DME) is often assessed separately from DR because its course of progression can run independently from that of DR.

The risk of development and progression of DR is closely related to the type and duration of diabetes and levels of blood glucose, blood pressure, and possibly lipids.[3] Pathways key to the development of DR include[3]:

- Increased polyol pathway
- Activation of protein kinase C (PKC)
- Increased expression of growth factors (eg, vascular endothelial growth factor [VEGF] and insulin-like growth factor-1)
- Hemodynamic changes
- Accelerated formation of advanced glycation end products (AGEs)
- Oxidative stress
- Activation of the renin-angiotensin system (RAS)
- Subclinical inflammation and capillary occlusion

Currently, the most widely studied growth factor in relation to diabetic retinopathy is VEGF.3 This molecule stimulates endothelial cell (EC) growth and neovascularization, promotes angiogenesis, causes breakdown of the blood-retinal barrier (BRB), and increases vascular permeability in the ischemic retina.

The hallmark retinal microvascular signs of NPDR include hemorrhages, hard exudates (lipid deposits), cotton-wool spots, microaneurysms (MAs), venous dilation, venous beading, venous loop formation, and intraretinal microvascular abnormalities (eg, dilated capillaries).[3, 4] Mild NPDR is characterized by MAs only, whereas moderate NPDR adds other microvascular lesions.[2] Severe NPDR involves >20 intraretinal hemorrhages in 4 quadrants, venous beading in ≥2 quadrants, or intraretinal microvascular abnormalities in 1 or more quadrant. Increasing severity of NPDR requires more frequent examinations (eg, every 3-6 months for severe NPDR).

References

1. National Eye Institute. Vision loss fromeye diseases will increase as Americans age. http://www.nei.nih.gov-/news/pressreleases/041204.asp. Accessed October 21, 2015.

2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet.* 2010;376:124-136.

3. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of diabetic retinopathy. *ISRN Ophthalmol.* 2013;2013:343560.

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

	Description	Assessment Considerations
Microaneurysms	Isolated, spherical, red dots of varying size. They may reflect an abortive attempt to form a new vessel or may simply be a weakness of a capillary vessel wall through loss of normal structural integrity.	They are easiest seen on fluorescein angiography (FA).
Dot hemorrhages	Dot hemorrhages cannot always be differentiated from microaneurysms because they are similar in appearance but with varying size.	The term dot hemorrhage/ microaneurysm (H/MA) is often used.
Blot hemorrhages	Formed where clusters of capillaries occlude leading to formation of intraretinal blot hemorrhages.	The lesion can be seen in the outer plexiform layer on FA where it does not mask the overlying capillary bed unlike dot and flame hemorrhages, which lie more superficially in the retina.
Cotton wool spots	These represent the swollen ends of interrupted axons where buildup of axoplasmic flow occurs at the edge of the infarct.	These features are not exclusive to DR and do not in themselves appear to increase the risk of new vessel formation. For example, they may occur in hypertension HIV/AIDS.
Intraretinal microvascular anomalies	These are dilated capillary remnants following extensive closure of capillary networks between arteriole and venule. Associated features include: • Venous beading (foci of venous endothelial cell proliferation that have failed to develop into new vessels) • Venous reduplication (rare), • Venous loops (thought to develop because of small vessel occlusion and opening of alternative circulation) • Retinal pallor and white vessels	They are easiest seen on FA.
Macular changes in NPDR: • Macular edema • Macrovascular disease	Thickening of retina takes place because of accumulation of exudative fluid from damaged outer BRB (extracellular edema) or as a result of hypoxia, leading to fluid accumulating within individual retinal cells (intracellular edema). It may be focal or diffuse. Flame hemorrhage and cotton wool spot formation. May occur due to arteriolar occlusion, without capillary occlusion, which frequently affects the horizontal nerve fiber layer of the retina.	The appearance of macular edema can be appreciated on stereoscopic examination or inferred by the presence of intraretinal exudate.
Optic disc changes	Occasionally swollen optic discs may be seen (diabetic papillopathy) in diabetic patients.	In diabetic papillopathy, vision is usually not significantly impaired.

Table 2. Classification of diabetic retinopathy by severity

From Cheung et al., 20102

			Frequency of examination
No retinopathy	No microvascular lesions	Low risk of progression to vision-threatening retinopathy	Once every 1-2 years
Mild NPDR	Microaneurysms only	5% (within 1 year) and 14% (within 3 years) progress to PDR	Yearly
Moderate NPDR	Microaneurysms and other microvascular lesions, but not severe NPDR	12%-26% (within 1 year) and 30%-48% (within 3 years) progress to PDR	Every 3-6 months
Severe NPDR	More than 20 intraretinal hemorrhages in 4 quadrants or venous beading in 2 or more quadrants, or intraretinal microvascular abnormalities in 1 or more quadrants but not PDR	2% (within 1 year) and 71% (within 3 years) progress to PDR	Every 3-6 months
PDR	Neovascularization of 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; moderate NVE with vitreous hemorrhage	Indication for panretinal photocoagulation; urgent if high-risk characteristics are present	Variable
CSME	Retinal thickening within 500 µm from center of macula; hard exudates within 500 µm from center of macula with adjacent retinal thickening; retinal thickening of more than 1 optic disc area within 1 optic disc diameter from center of macula	Can develop at any stage of diabetic retinopathy; indication for macular laser	Variable