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Diabetic retinopathy

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Chapter 8

Optical coherence tomography and OCTA for the diagnosis of diabetic macular edema

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8.1 Introduction to DME

Background and epidemiology: Diabetes mellitus (DM) and its vascular complications, including retinal damage known as diabetic retinopathy (DR), have been studied for the past century. The CDC predicts up to 33% of the United States (US) population will have DM by the year 2050 and a portion of these patients will suffer sight-threatening complications such as retinopathy and macular edema [1]. Over the last decade, technological advances in retinal imaging and novel therapeutics have vastly improved the evaluation, management, and outcomes of patients with DR and diabetic macular edema (DME) [2]. For most diabetic patients, retinopathy develops within 10–15 years after initial diagnosis [2]. DR is the leading cause of vision loss in the US in patients between 25 and 74 years of age affecting approximately 4.2 million adults, with approximately 655 000 having vision-threatening DR [3]. Progression of DR can lead to vision loss, often secondary to macular edema, hemorrhage from neovascularization, retinal detachment, or neovascular glaucoma.

Diabetic macular edema, a complication of DR, is one of the leading causes of visual impairment in the US and is the most common cause of vision loss in patients with DR [1, 4]. In the US, the overall prevalence of DME is 3.8% and affects approximately 750 000 individuals [5]. The prevalence of DME in patients with type 1 DM (T1DM) and type 2 DM (T2DM) is 14% and 6%, respectively [6]. Prolonged diabetes, elevated hemoglobin A1c concentrations, and longstanding hyperglycemia are associated with a greater risk for development of DR and DME [5].

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Definitions: Diabetic retinopathy encompasses a spectrum of diseases. The classification of DR is categorized by assessment for abnormal retinal vascularization and its severity [7]. Although the stratification of the disease has been useful for studying the effects of treatment and early diagnosis, each patient with DR exhibits a unique presentation of symptoms, imaging, clinical findings, and rate of progression, necessitating a personalized approach to their management [8].

Nonproliferative diabetic retinopathy (NPDR) is defined by abnormalities in the retinal vasculature, ranging from mild cases that only involve microaneurysms to moderate and severe cases that involve additional vascular abnormalities described in table 8.1 [8] The pathophysiology of retinal neovascularization stems from a state of chronic hyperglycemia. Hyperglycemia damages retinal capillaries, weakening

Table 8.1. Diagnostic criteria for nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, clinically significant macular edema, and diabetic macular edema.

Nonproliferative diabetic retinopathy		
	Mild	– Microaneurysms with no other retinal findings
	Moderate	– Increased number of microaneurysms and dot-blot hemorrhages – May have presence of cotton wool spots, venous beading, and hard exudates – Does not meet severe NPDR criteria
	Severe	– Microaneurysms and severe intraretinal hemorrhages **and** – microaneurysms in all 4 retinal quadrants **or** – definite venous beading in ⩾2 quadrants **or** – moderate intraretinal microvascular abnormalities in ⩾1 quadrant
	Very Severe	– If ⩾2 of severe NPDR criteria and does not meet PDR criteria
Proliferative diabetic retinopathy		
	Early	– Neovascularization **without** meeting high-risk PDR criteria
	High-risk	– Neovascularization of the disk ⩾1/3 to ½ disk area **or** – Neovascularization of the disk and vitreous hemorrhage or the presence of preretinal hemorrhage **or** – Neovascularization in other parts of the retina that is >1/2 disk area **with** the presence of vitreous or preretinal hemorrhage

	Severe	– -Preretinal or vitreous hemorrhage obscuring the posterior fundus – -Detachment of the center of the macula
Clinically significant macular edema		– Retinal thickening ⩽500 microns from the center of the macula **or** – Presence of hard exudates and retinal thickening **or** – Presence of retinal thickening that is ⩾ 1 disc area in size that is located ⩽ 1 disc diameter from the foveal center – Can occur at any stage of NPDR and PDR
Center-involved DME		– Retinal thickening in the macula **involving** the central subfield zone (1mm in diameter)
Non-center involved DME		– Presence of retinal thickening in the macula **NOT** involving the central subfield zone (1mm in diameter)

the vessel walls which can lead to the formation of microaneurysms. When the microaneurysms rupture, they can cause hemorrhages in the deeper layers of the retina (i.e., inner nuclear and outer plexiform layers) confined superficially by the internal limiting membrane.

- Mild NPDR—microaneurysms with no other retinal findings.
- Moderate NPDR—presence of microaneurysms and other vascular abnormalities like dot-blot hemorrhages, cotton wool spots, venous beading, and hard exudates, but does not meet the criteria for severe NPDR classification.
- Severe NPDR—microaneurysms and severe intraretinal hemorrhages with microaneurysms in all four retinal quadrants, definite venous beading in more than two quadrants, or moderate intraretinal microvascular abnormalities (IRMA) in at least one quadrant. Severe NPDR does not meet the additional criteria for proliferative diabetic retinopathy. Within one year, 52%–75% of patients in the severe NPDR category will progress to PDR [8].

Proliferative diabetic retinopathy (PDR) is defined by the presence of retinal neovascularization. In PDR, the pathophysiology of neovascularization is a response to retinal ischemia. Angiogenic factors, one of which being vascular endothelial growth factor (VEGF), are released to stimulate the formation of new retinal vessels to compensate for the hyperglycemia-induced vessel damage. An important characteristic of PDR is that neovascularization extends beyond the internal limiting membrane and leads to growth into the vitreous. Fibrovascular contractile membranes can form in the vitreous and cause traction on the retina which can progress into tractional retinal detachment. Severity of PDR is further categorized by degree of neovascularization of the disc, presence of vitreous or preretinal hemorrhage, and detachment of the macula.

Diabetic macular edema (DME) is defined by thickening of the retina near the macula or the presence of hard exudates with adjacent retinal thickening. DME was historically classified as focal versus diffuse based on diagnostic criteria for clinically significant macular edema (CSME), as defined by the ETDRS (table 8.1) using information gathered by slit-lamp exam. DME involving the fovea was shown in the Early Treatment of Diabetic Retinopathy Study (ETDRS) to have a 24% risk of developing moderate visual loss if left untreated.

With the development of optical coherence tomography, DME is now defined by the presence of foveal edema, categorized as 'center-involved' or 'not center-involved'. DME can occur at any stage of DR, in both nonproliferative and proliferative diabetic retinopathy, with increasing frequency as the severity of DR progresses [1]. Symptoms of vision loss are dependent on the location of the edema. DME that is not center-involved is usually asymptomatic. However, patients with center-involved DME often experience progressive vision loss on the timescale of weeks to years after the initial onset of symptoms [1].

Pathophysiology: The development and progression of diabetic retinopathy occurs as a direct consequence of diabetes mellitus and hyperglycemia causing pathology of the retinal vessels [1]. The two principal changes in the retinal vasculature from DR are abnormal permeability and occlusion leading to ischemia and subsequent neovascularization [1, 9]. Early in the disease, hyperglycemia-induced damage to the vasculature can occur prior to the onset of clinical signs. Later in the disease, overactivity of angiogenic factors like vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1) lead to the progression from NPDR into PDR or DME [10]. The variability in these factors and their subsequent response to hyperglycemia is thought to explain the spectrum of the severity, rate of development, and rate of progression of DR and DME in patients with DM despite adequate glucose control [9, 10].

Structural anatomic retinal changes—Anatomic changes in the retina due to diabetes include retinal pericyte loss, thickening of the capillary basement membrane, and microaneurysms of the capillary walls. The anatomical changes increase the susceptibility of the retinal capillaries and arterioles to become nonperfused, leading to retinal ischemia and disruption of the blood-retinal barrier. In response to the disruption of the vasculature, there is an increase in vascular permeability leading to retinal edema. As the retinal ischemia worsens, the risk for retinal traction and potential detachment increases [7].

Retinal microthrombosis—the formation of retinal microthrombosis in the retinal vessels can lead to occlusion of the capillaries and capillary leakage. One of the first signs of change in the retina prior to clinically detectable DR is adhesion of leukocytes to the retinal vascular endothelium, hypothesized to contribute to increased vascular permeability. The loss of endothelial integrity contributes to retinal ischemia, leading to release of endothelial growth factors such as IGF-1, VEGF, fibroblast growth factor (FGF), and platelet derived growth factor (PDGF) that induce vascular proliferation and angiogenesis [7].

Altered retinal blood flow—Physiologic retinal blood flow is kept constant by an autoregulated mechanism until the mean arterial pressure is raised 40% above

baseline. In patients with chronic hyperglycemia, this autoregulation mechanism is thought to be impaired, leading to a sustained increase in retinal blood flow causing increased shear stress on the retinal blood vessels. The pathologic environment is also thought to increase the stimulation of vasoactive substances leading to vascular leakage and accumulation of fluid in the outer layers of the retina which can progress to macular edema [11].

Growth factors: Damage to the retinal vessels leads to release of growth factors and subsequent neovascularization. The process of neovascularization is thought to be from the interaction of IGF-1 and VEGF. The role of IGF-1 was shown in experiments that demonstrated an increase in neovascularization in the year following the initiation of intensive insulin therapy, as insulin stimulates IGF-1 [10]. Furthermore, studies have shown that decreases in IGF-1 concentrations via injury to the pituitary or hypophysectomy leads to decreases in neovascularization, with the potential to reverse advanced retinal disease [10].

VEGF is an angiogenic growth factor and vascular permeability factor that is thought to play a significant role in the pathogenesis of DR and DME. Studies have demonstrated a positive correlation between the immunostaining intensity for VEGF and the severity of retinopathy [11].

Elevated erythropoietin (EPO) has also been shown to cause retinal angiogenesis in DR with increased concentrations found in the vitreous fluid of patients with DR [5].

Currently known risk factors for the development and progression of DR and DME include chronicity of diabetes, hemoglobin A1c, hypertension, nephropathy, and dyslipidemia.

Modifiable Risk Factors: Clinical trials and epidemiological studies show that the two most important modifiable risk factors in the development of DR and DME are blood sugar and blood pressure control [12]. Strict blood glucose control with HbA1c <7% can lead to sustainable and potent protective effects against the development of DR and DME in both type 1 and 2 DM. Moreover, the Diabetes Control and Complications Trial showed that strict blood glucose control decreases the incidence of retinopathy by up to 76% and decreases the progression of mild DR to severe DR by up to 54% [12]. Thus, control of hyperglycemia has a great effect on preventing or delaying onset as well as preventing progression of DR. Likewise, strict blood glucose control demonstrated a 46% reduction in the incidence of DME [12]. Controlling hyperglycemia should be carefully managed to avoid causing hypoglycemia, particularly in the elderly population. The ADVANCE and the Veterans Affairs Diabetes Trial studies concluded that more intensive glycemic control, with target HbA1c < 6.5%, did not have a significant further reduction in the incidence of DR or disease progression [13, 14].

Although the link between hypertension and dyslipidemia and the development of DR and DME are weak, careful management can reduce the risk of other diabetic complications such as nephropathy and cardiovascular diseases [13]. The UK Prospective Diabetes Trial concluded that tight blood pressure control (BP < 150/85 mmHg) in patients with type 2 DM reduced the risk of developing microvascular disease by 37% and decreased the rate of DR progression by 34% [15]. However, the risk reduction in disease progression waned after stopping intensive blood pressure control

and studies have not been able to show a risk reduction in DR incidence with management of hypertension [15]. Thus, the treatment of hypertension for the sole purpose of reducing DR incidence and progression is not currently recommended but should be initiated for control and prevention of microvascular complications from DM, particularly nephropathy.

Smoking is a modifiable risk factor that has been shown to increase the prevalence and rate of progression of DR in patients with type 1 DM. However, its role as a risk factor in patients with T2DM is disputed, with studies from the United Kingdom Prospective Diabetes Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy demonstrating no association of smoking with increased prevalence or progression of DR [16].

Non-modifiable risk factors: Studies have shown that patients with both type 1 and type 2 DM have an increased risk of developing DR and DME with increased duration of disease, independent of their glycemic control. Patients with type 1 DM will likely develop DR after a certain duration of disease, but the results are less clear for type 2 DM, likely due to competing risks of mortality [17].

Puberty has been shown to increase the risk for developing DR, particularly in patients with type 1 DM. Pre-pubertal exposure to either type 1 or type 2 DM increases the risk of developing DR. However, type 1 DM during puberty has a greater impact on risk for developing DR [17]. Moreover, the onset of type 1 DM during or post puberty increases the risk of developing severe DR compared to patients with disease onset during their pre-pubertal years.

Pregnancy increases the risk of developing DR by 3 times in patients with type 1 DM versus patients with type 2 DM. However, the development of DR in pregnancy is often transient and patients typically demonstrate resolution and regression of DR in the postpartum period. There is no significant difference in the prevalence of DR when comparing patients who had been pregnant compared to those who had not been pregnant [17].

Symptomatic presentation and physical examination—Patients with DM should receive annual ophthalmic evaluations if they either do not have retinopathy or have mild NPDR to monitor progression, as DR is often asymptomatic regardless of disease severity. It is important to note that mild to severe DME can be present even without symptoms noticeable to the patient, and the possibility of progression to DME in any stage of DR further necessitates ophthalmic examinations. A thorough documentation of the patient's history of diabetes, medications, A1c trends, diet, and the presence of other complications of diabetes such as hypertension, hypercholesterolemia, renal disease, and thyroid disease is critical in the evaluation. As most early stages of DR are asymptomatic, the presence of symptoms may be a sign of more advanced disease, thus screening examinations are critical to achieve early diagnosis. Symptomatic patients may experience blurred vision, narrowed field of vision, flashes, floaters, elevated intraocular pressure in the case of neovascular glaucoma, and difficulty with night vision. The index for suspicion of DR and DME increases in patients with recent vision impairment, particularly in the setting of chronic diabetes and hyperglycemia, nephropathy, hypertension, or dyslipidemia.

On physical examination, patients receive a biomicroscopic examination using a slit lamp microscope and indirect ophthalmoscope. Historically, DME was categorized by guidelines established by the ETDRS to define clinically significant macular edema (CSME). The criteria for the diagnosis of CSME are in table 8.1. The diagnosis of CSME using the ETDRS criteria was thus a clinical diagnosis made via slit lamp exam findings. The importance of detecting CSME via conducting a careful physical exam was highlighted from ETDRS data showing that patients with type 2 DM with severe NPDR had a 50% chance of developing high-risk characteristics for vision loss if they did not receive laser treatment. Consequently, a diagnosis of CSME using ETDRS criteria was used to prevent a high percentage of visual loss by initiating laser, pharmacological, or surgical treatment.

With the advent of anti-VEGF therapy in recent years and advances in imaging with optical coherence tomography, the ETDRS criteria has become relatively obsolete. DME is classified more practically now as fovea-involving vs. non fovea-involving, as fovea-involving DME poses a greater risk for development and progression of visual loss and are candidates for anti-VEGF therapy.

Overview of diagnostic procedures, laboratory testing, differential diagnosis: Diagnosis of diabetic retinopathy is based on the findings from the retinal exam by direct/indirect fundoscopy, fundus photography, slit lamp biomicroscopy, and undilated gonioscopy (to assess neovascularization of the iris neovascularization or in the presence of elevated intraocular pressure). A full ocular exam should be performed to assess visual acuity, pupillary response, and intraocular pressure. Dilated visual exams are performed to assess for degree of retinopathy, including microaneurysms, intraretinal hemorrhages, venous dilation, cotton wool spots, retinal thickening, lipid deposits, venous dilation/beading/loops, and intraretinal microvascular abnormalities. Further assessment of the retina if deemed necessary can include fluorescein angiography (FA), ultrasound, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) [9, 18, 19].

FA is a valuable imaging tool to aid in the diagnosis and management of DR and DME as it can detect microaneurysms, dot and blot hemorrhages, areas of nonperfusion, and presence of neovascularization. FA images distinguish microaneurysms, which appear hyperfluorescent, from dot and blot hemorrhages, which appear hypofluorescent. Nonperfused areas are detected on FA as homogenous hypofluorescent patches. Neovascular tufts often leak dye because of their weaker vessel walls and higher vascular permeability, which are identified on FA as hyperfluorescent areas that increase in size and intensity as the test phase progresses. FA also helps to identify the location of microaneurysm leakage for laser therapy.

Screening: The American Diabetes Association (ADA) and American Academy of Ophthalmology (AAO) have the following DR and DME screening recommendations for patients with DM:

- For patients with type 1 DM, an initial dilated and comprehensive eye exam is recommended within 5 years of onset of diabetes.
- For patients with type 2 DM, a comprehensive dilated eye exam is recommended at the onset of diabetes.

- For type 1 and type 2 DM, annual follow-up eye exams are recommended.
- Screening should continue regularly during pregnancy, at each trimester of pregnancy, and 1 year postpartum depending on the severity of retinopathy. Gestational diabetes does not appear to increase the risk of developing DR [18, 19].

Laboratory testing: Routine measurements of A1c and lipid panel (LDL, HDL, TG) levels (table 8.2).

Differential diagnosis: The differential diagnosis for DR and DME are presented in table 8.2.

Follow-Up Care: Frequent follow-up visits and dilated ophthalmic examinations, especially in at-risk patients with DR, can prevent vision loss and reduce the cost of treating more advanced disease [20]. The AAO guidelines for follow-up exams are listed in table 8.3.

Complications and Prognosis: Diabetic retinopathy is the most common cause of new onset blindness in adults. The vision loss due to DR is associated with a significant economic burden for patients and their families [18]. Diabetic retinopathy can progress in severity if left untreated. Progression includes transition from NPDR to PDR, worsening vision, and increased risk of blindness. The risk of progression to proliferative diabetic retinopathy within 1 year is 5% with mild NPDR, 20% with moderate NPDR, and 50% with severe NPDR [7].

Table 8.2. Differential diagnosis for DR and DME[19].

Leading Diagnosis	Differential Diagnosis
Macular Edema	– Hypertensive retinopathy – Retinal vein occlusion – Microaneurysm rupture – Radiation – Irvine-Gass syndrome – Subfoveal choroidal neovascularization
Nonproliferative DR	– Central/branch retinal vein occlusion – Ocular ischemic syndrome – Hypertensive retinopathy – Radiation retinopathy
Proliferative DR	– Neovascular complications of central retinal artery or vein occlusion – Branch artery or vein occlusion – Sickle cell retinopathy – Embolization from IV drug use – Sarcoidosis – Inflammatory conditions (i.e. SLE) – Complications from ocular ischemic syndrome – Hypercoagulable states (i.e. antiphospholipid syndrome) – Radiation retinopathy

Table 8.3. AAO guidelines for follow-up care based on severity of DR and DME.

Stage of DR	No DME or CSME	DME present	CSME present
No Diabetic Retinopathy/ Mild NPDR	Annual dilated exams	Follow-up every 4–6 months	Follow-up every month
Moderate NPDR	Follow-up every 6–12 months	Follow-up every 3–6 months	Follow-up every month
Severe or Very Severe NPDR	Follow-up every 4 months	Follow-up every 2–4 months	Follow-up every month
PDR	Follow up every 4 months	Follow-up every 4 months	Follow-up every month
High-Risk PDR	Follow-up every 4 months	Follow-up every 4 months	Follow-up every month

Vitreous hemorrhage as a complication of proliferative diabetic retinopathy is a cause of severe vision loss and occurs due to rupture of blood vessels in the vitreous. Vitreous hemorrhage occurs from upregulation of angiogenic factors like IGF-1, VEGF, and FGF in the vitreous, fibrovascular membranes, and from the retina due to hypoxic conditions of DR leading to formation of neovascular buds from retinal blood vessels. The neovascularized tissue can proliferate and invade the space between the retina and the posterior hyaloid face producing firm adhesions. As the vessels continue to proliferate, their fibrous component subsequently increases. Contraction of the fibrous component generates traction on the posterior hyaloid face and pulls on the weak and friable neovascular tissue on the retina leading to a vitreous hemorrhage [21].

Vitreous hemorrhage can lead to further fibrosis and contraction of the vitreous, which can lead to another vision-threatening complication of DR: tractional retinal detachment (TRD). TRD is the separation of the retina from the retinal pigment epithelium due to traction from the vitreous or retinal surface. Diabetes and DR are the most common causes of RTD [22].

8.2 Development/history of OCT use in DME

The role of imaging for the management of diabetic macular edema began with fluorescein angiography (FA), first described in 1961 and later adapted into standard practice within the field of ophthalmology [23]. In patients with DME, FA demonstrates patterns of hyper-fluorescence, representing the breakdown of the blood-retinal barrier. In eyes with CSME that may be candidates for laser photocoagulation therapy, FA was utilized to identify the leaking microaneurysms and locate the areas of diffuse leakage to be targeted for therapy. However, major limitations of FA are the inability to quantify the amount of leakage and discriminate depth-dependent pathology between the superficial versus the deep capillary plexuses, rendering it less clinically useful when monitoring response to therapy [24].

Optical coherence tomography (OCT) is a noninvasive imaging modality that produces cross-sectional images of optical reflectivity of the retina [25]. The advent of OCT into the clinical setting revolutionized the management of DME. OCT has been increasingly used for the diagnosis of DR and for monitoring disease progression because of its ability to measure retinal thickness directly and reliably from the tomogram by either measuring the inner and outer boundaries of the retina manually, or by using computer-aided image processing algorithms [25]. OCT also provides the capability for morphologic assessment of the macula, with several anatomic patterns that have been reported in DME. Moreover, the objective output of OCT allows for quantification of cell layer thickness and macular volume, enabling longitudinal assessments to demonstrate and monitor response to therapy, a quality that makes it superior to FA in its clinical utility.

The development of OCT began with time-domain OCT, which uses interferometry-based technology to generate images with an axial resolution of 10 um, and was first used in a clinical setting in 1993 for retinal imaging [26, 27]. TD-OCT was utilized in clinical trials to monitor and quantify the benefits of anti-VEGF therapy for DME by evaluating central subfield thickness of the retina to aid in making retreatment decisions.

In the 2000s, spectral-domain OCT (SD-OCT) was developed as the next-generation alternative to TD-OCT. SD-OCT utilizes a spectrophotometer and the Fourier transform to generate images with a higher axial resolution of 5 um along with faster acquisition speeds, making the cell layers of the macula more distinctive [28]. With the advances brought forth by SD-OCT, ophthalmologists have been provided with more information to help guide clinical management than what was previously available with TD-OCT [28]. SD-OCT is currently the most commonly used and commercially available imaging device for the diagnosis and management of DME.

The breakthrough with SD-OCT along with the improvements in available laser technology in recent years paved the way for the development of swept-source-OCT (SS-OCT), a variation of SD-OCT. SS-OCT utilizes a photodetector instead of a spectrometer, and uses swept-source lasers that have increased scanning speeds capable of up to a million A-scans per second, which provides a high-density scan that produces higher resolution en face OCT images. SS-OCT has the benefit of improved visualization of the choroidal-scleral surfaces and identifying structures below the retinal pigment epithelium. The high-resolution properties of SS-OCT are promising but its use is currently limited to research settings and is not yet commercially available, limited by high cost, availability, and lack of clear clinical advantages over SD-OCT. SS-OCT devices may see increased prevalence in clinical applications beyond ophthalmology, including cardiology, dermatology, and gastroenterology.

8.3 Pathology and mechanism of OCT findings in DME

Optical coherence tomography (OCT) is a diagnostic imaging technique that is analogous to B-scan ultrasound by using optical interferometry to resolve the

distances of reflective structures within tissues by using light instead of sound [29]. OCT images are two-dimensional data sets that represent the optical backscattering within a cross-sectional plane through the target tissue. The first step in reconstructing a tomographic image is the measurement of the axial distance, or the range of information within the target tissue. OCT essentially images by measuring the echo time delay and intensity of backscattered or backreflected light from the unique internal microstructure in materials or tissues of interest [28, 29]. The measured optical backscattering or backreflection in a cross-sectional plane or volume allows OCT images to reflect a two-or-three-dimensional data set, respectively. Two important imaging characteristics are image resolution and imaging depth. The resolution of OCT depends directly on the frequency or wavelength of the light source used; thus, the inherently high resolution of OCT allows identification of tissue architectural morphology features [27, 29]. Unlike ultrasound, where the velocity of sound in water is approximately 1500 m s^{-1}, the velocity of light is approximately 3×10^8 m s^{-1}, which means the measurement of the echo time delay with light cannot be measured with direct electronic detection. Therefore, OCT utilizes low-coherence interferometry to measure the echo time delay. In the older generation time-domain OCT (TD-OCT), low-coherence interferometry measures the echo time delay and intensity of the backscattered light from tissue by comparing it to light that has traveled a known reference path length and time delay [30]. This is accomplished with a Michelson-type interferometer, where a light source is directed into a beam splitter that sends one of the beams as the incident light source into the tissue sample to be imaged, while the second beam travels a reference path with a variable path length and time delay [30]. The backscattered light from the sample is then interfered with the reflected signal from the reference arm and detected with a photodetector at the output of the interferometer. Based on the coherence pattern, the echo time delay and intensity of backscattered light from the sample arm can be measured by comparing it with the reference path length [30].

In spectral-domain OCT, the schematic is similar to TD-OCT, but the reference arm is immobilized, and the detector is replaced by a spectrometer, allowing for the capability to collect signals from all depths of the sample throughout the entire acquisition time. A Fourier transform of the spectral measurement converts the detected backscattered signals from the imaged tissue into the frequency domain, which represents the tissue depth reflectivity profile. SD-OCT includes a host of advantages over TD-OCT including that of faster scanning times, higher resolution, greater field-of-view, and increased signal-to-noise ratio [31].

8.4 Findings identified on OCT in the diagnosis of DME

See figures 8.1–8.9 for findings identified on OCT in the diagnosis of DME.

ILM = internal limiting membrane
NFL = nerve fiber layer
GCL = ganglion cell layer
IPL = inner plexiform layer
INL = inner nuclear layer

Figure 8.1. OCT showing a normal foveal contour. The layers of the retina from anterior to posterior are listed below.

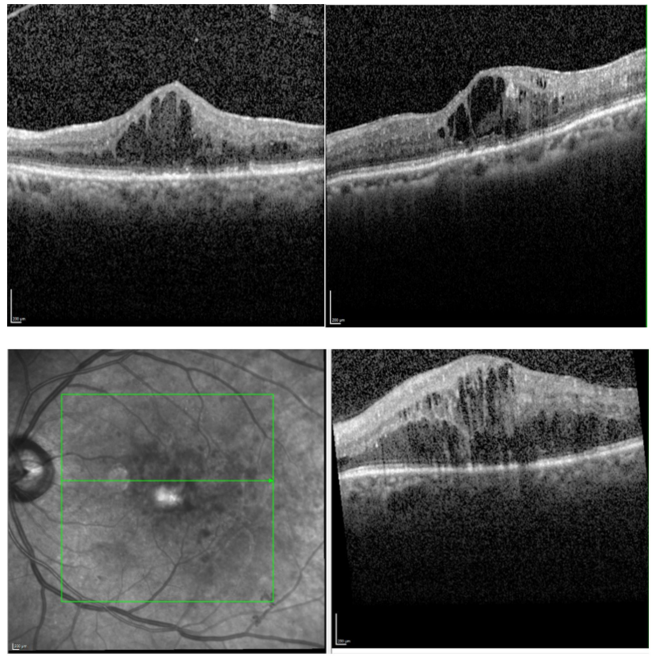

Figure 8.2. Intraretinal fluid (IRF) is a result of damaged, leaky vessels as a result of diabetic microvascular changes. IRF appears as dark cystic spaces within the retinal layers which can often distort the foveal contour. Center-involving edema warrants treatment.

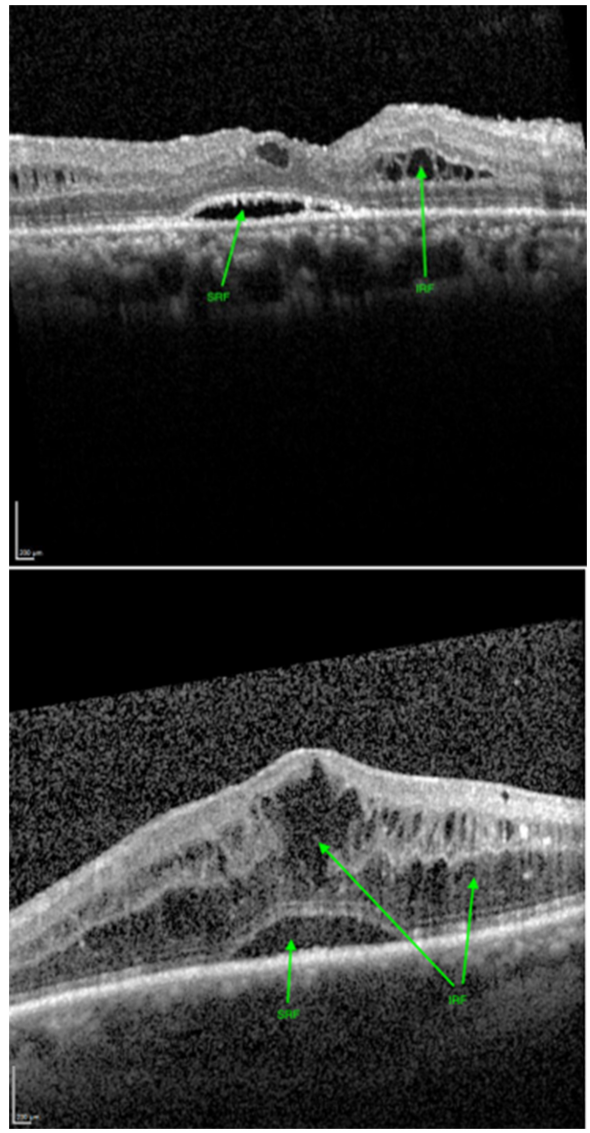

Figure 8.3. Fluid can also build up underneath the retina above the RPE. Below are examples of **subretinal fluid** (SRF) with adjacent and overlying intraretinal fluid with foveal contour distortion.

OPL = outer plexiform layer
ONL = outer nuclear layer
ELM = external limiting membrane
IS/OS junction = photoreceptor layer
RPE/Bruch's complex
Choroid

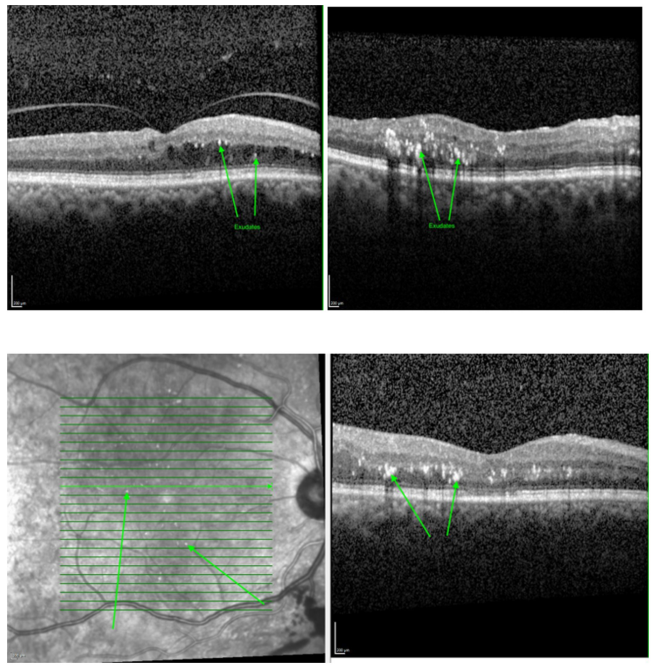

Figure 8.4. Exudates can be seen on OCT as hyperreflective foci. They are composed of lipid and protein materials that leak from impaired blood vessels or aneurysms and are commonly found in the outer plexiform layer.

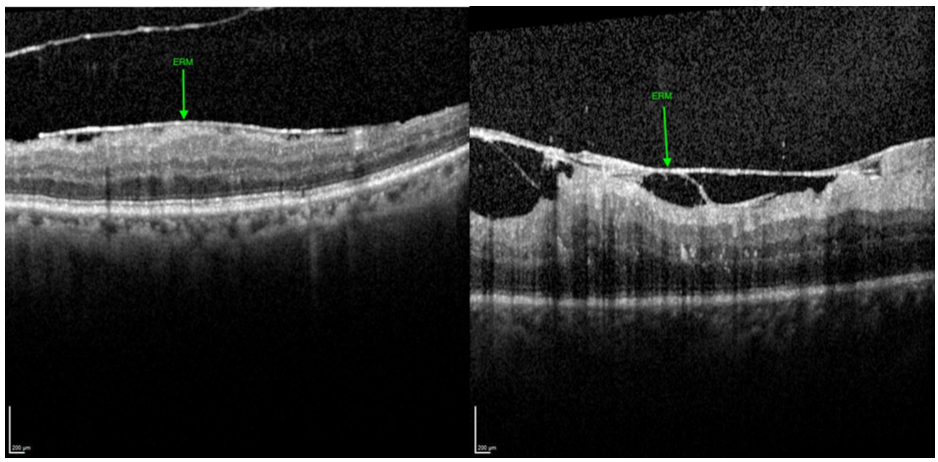

Figure 8.5. Epiretinal membranes are often seen as a complication of diabetic retinopathy from inflammation. They represent the proliferation of glial cells that overtime can cause traction of the retina leading to various degrees of visual distortion and decreased vision.

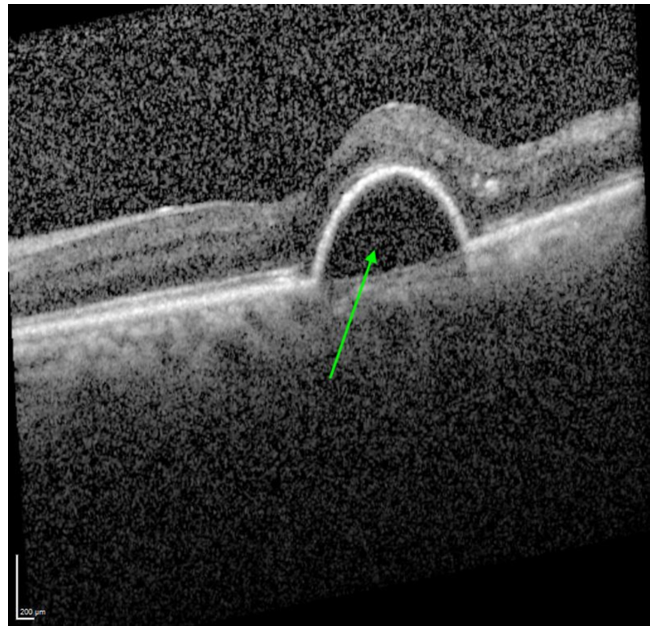

Figure 8.6. Fluid can also develop underneath the pigment epithelium and is known as a **pigment epithelium detachment** (PED)

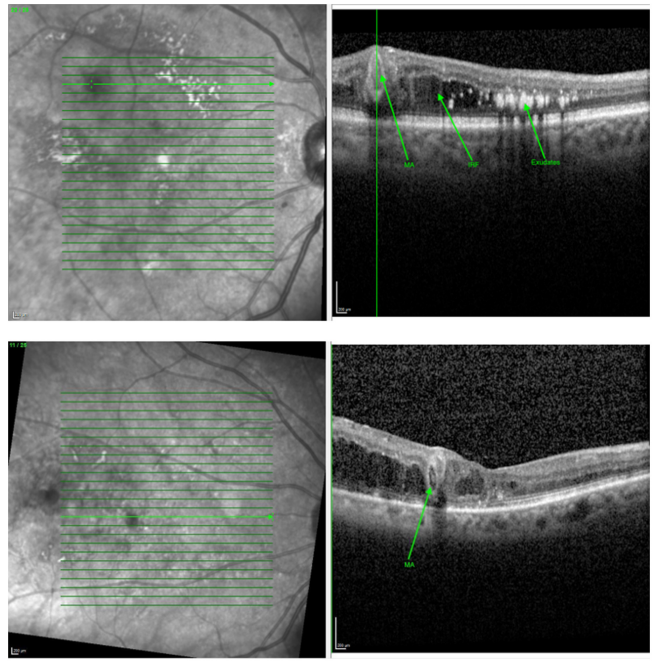

Figure 8.7. Microaneurysms (MA) can be seen clinically as well as on OCT. Leaking aneurysms will develop surrounding intraretinal fluid often combined with exudates in a circinate pattern surrounding the MA.

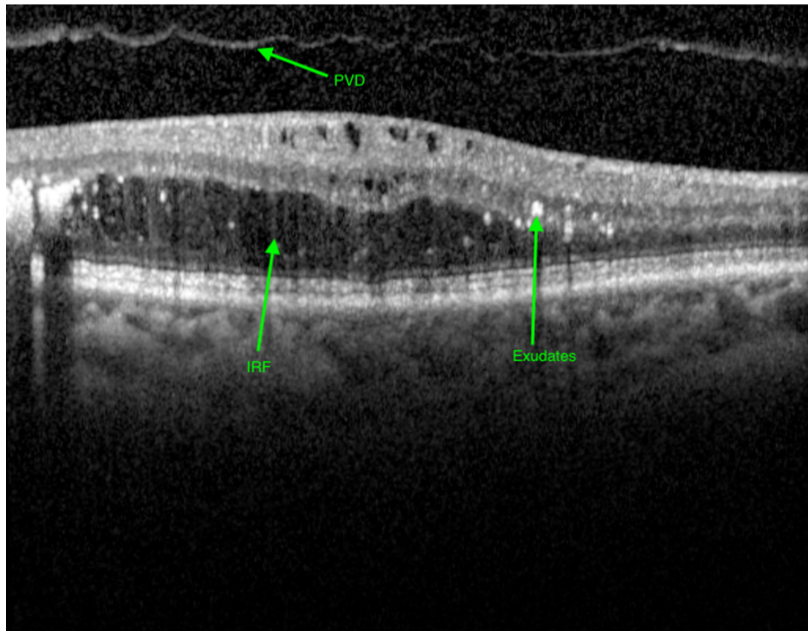

Figure 8.8. Separation of the posterior hyaloid membrane from the retina is known as a **posterior vitreous detachment (PVD)** which can often be seen on OCT within the vitreous. This is an example of a complete PVD.

8.5 Classification and grading of OCT findings in DME

Prior to OCT technology, edema was graded clinically on fundoscopic examination for clinically significant macular edema (CSME), strict criteria used in the ETDRS trials. With the widespread availability of OCT technology, DME involving the center of the macula (defined as retinal thickening in the macula involving the central subfield zone 1 mm in diameter) is the main criteria for treatment of DME, versus non-center involved (retinal thickening that does not involve the central subfield zone).

Additionally, several OCT biomarkers have demonstrated prognostic value including disorganization of the retinal layers (DRIL), ellipsoid zone disruption, and vitreomacular interface abnormalities. These features have been shown to be associated with poor outcomes despite anti-VEGF treatment.

8.6 Introduction and development of OCTA in the diagnosis of DME

OCT has revolutionized retinal imaging for the diagnosis and management of diabetic retinopathy (DR) and diabetic macular edema (DME). However, OCT is unable to provide direct information about structural and functional changes in the retinal and choroidal vasculature such as blood flow velocity, differentiating afferent from efferent vessels, and detecting changes in vasculature permeability. Consequently, fluorescein angiography (FA) and indocyanine green angiography remain the gold standard for structural visualization and monitoring of dynamic changes of the retinal vasculature in DR and DME [32].

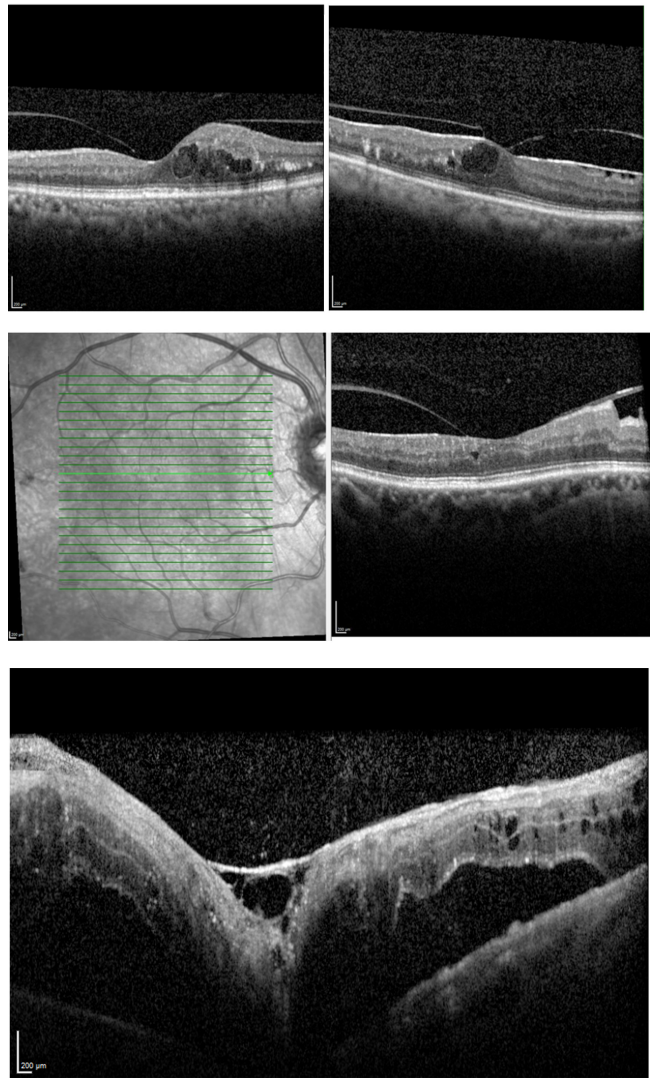

Figure 8.9. Vitreomacular adhesion (VMA) and **vitreomacular traction** (VMT) is when the posterior hyaloid has not fully detached and is still adherent to the retina. Traction in VMT can distort the foveal contour.

However, FA has several limitations including the inability to quantify leakage, discriminate between the superficial and deep capillary plexuses, administration of intravenous dye, and long acquisition times. To address the limitations of FA, OCT Angiography (OCTA) has been developed in recent years as a novel use of OCT technology to visualize the microvasculature of the retina and the choroid non-invasively. It is distinct from FA in that it does not necessitate the injection of fluorescein dye into a peripheral vein. With repeated scans at the same anatomic location, OCTA

can detect the changes in OCT reflectance signal from the flow through blood vessels, allowing for depth-resolved, motion-contrast imaging of the retinal vasculature. OCTA operates under the assumption that the only moving objects in the retina are the blood cells circulating through the vasculature. The identification of the moving blood cells translates to blood vessels in the final output images.

OCTA generates angiograms from different segments of the retina, typically including the superficial capillary plexus, deep capillary plexus, and the choriocapillaris. In healthy eyes, the deeper vasculature plexuses have a higher density of blood vessels compared to the superficial layers. In patients with DR, vascular abnormalities can be present in the different retinal layers. The ability to generate images of the retinal layers from superficial to deep vascular plexuses is the primary advantage of OCTA over fluorescein angiography, the latter of which focuses on superficial and larger retinal blood vessels [33]. In patients with DME and DR, OCTA can delineate the foveal avascular zone and identify areas of impaired blood flow when compared to FA. OCTA has been reported to identify changes in the microvasculature before clinically detectable DR or DME.

8.7 Pathology and mechanism of OCTA findings in DME

OCTA is designed based on OCT technology that allows for visualization of the functional vasculature in the eye. The mechanism of OCTA utilizes the variation in OCT signal from moving particles, such as red blood cells, as a contrast mechanism for imaging blood flow. By repeating multiple scans at the same anatomic location, temporal changes of the OCT signal caused by the moving particles generate the angiographic contrast and outputs the microvasculature visualization [33, 34].

OCTA has been shown to be comparable with FA and the clinical examination to identify vascular changes such as microaneurysms, impaired perfusion, retinal edema, vascular loops, intraretinal microvasculature abnormalities, and neovascularization [35]. Microaneurysms are detected on OCTA as hyperreflective spots, with further differentiation of the structural characteristics not seen by FA including fusiform, saccular, curved, or coiled shapes.

OCTA can assist in differentiating retinal neovascularization from intraretinal microvasculature abnormalities. Retinal and disc neovascularization is identified as interwoven vessels above the surface of the retina and the optic nerve [35]. Retinal neovascularization has been found to be adjacent to retinal capillary areas of nonperfusion, demonstrating that OCTA may have a role in distinguishing severe NPDR from PDR, and can be used for monitoring progression of severe NPDR (figures 8.10 and 8.11).

OCTA is also capable of identifying and distinguishing the foveal avascular zone (FAZ). The FAZ is the avascular area surrounded by foveal capillary circles at the center of the macula. Therefore, structural or perfusion abnormalities in the FAZ can greatly hinder visual acuity. In patients with DR, the FAZ is increased in size and is non-symmetrical due to loss of blood vessel integrity and damage to the capillary plexuses. Studies have shown that the grading of FAZ abnormalities is correlated with severity of DR. The FAZ was first identified by FA, but dye leakage

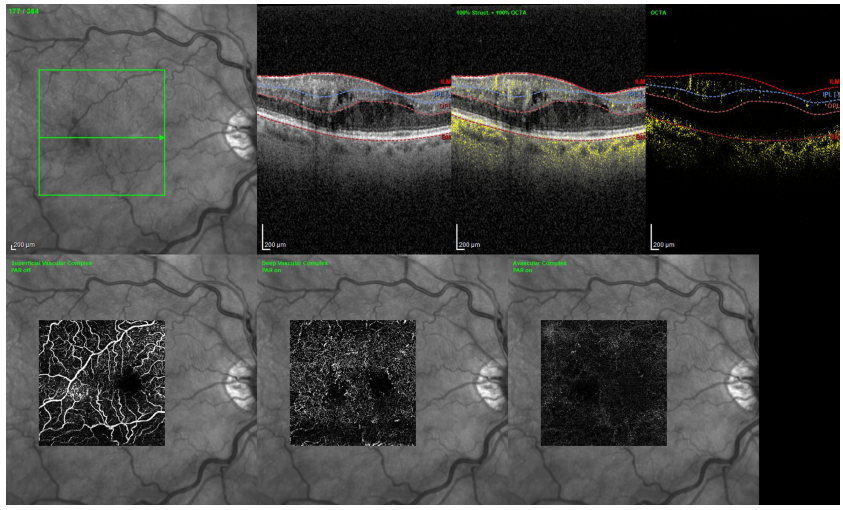

Figure 8.10. OCTA images from a patient with diabetic retinopathy with microaneurysms, impaired perfusion, and retinal edema.

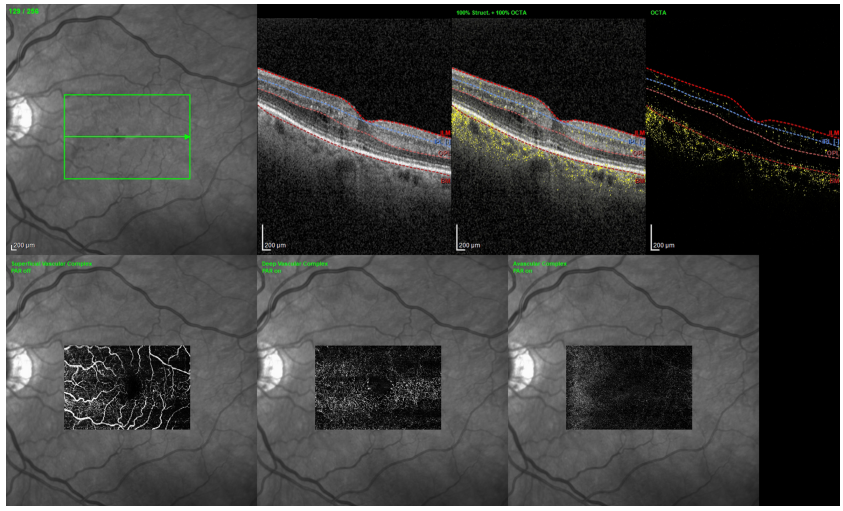

Figure 8.11. Example of OCTA in a healthy control eye.

often covered the FAZ. OCTA is now considered a superior option to FA to distinguish the FAZ and to characterize the central and parafoveal macular microvasculature [35].

OCTA's ability to distinguish areas of nonperfusion, alterations to the FAZ, and characteristics of microaneurysms may better help clinicians understand the pathophysiology of DME, improve grading of DME, and guide therapy decisions and management.

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