

Chapter

Optical Coherence Tomography and Optical Coherence Tomography Angiography Biomarkers in Diabetic Retinopathy

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Abstract

Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA) are essential tools for the diagnosis, treatment, and prognosis of diabetic retinopathy (DR) and diabetic macular edema (DME). OCT biomarkers, such as retinal thickness, intraretinal cystoid spaces, hyperreflective retinal foci, and disorganization of retinal inner layers, provide critical insights into disease severity and treatment response. OCTA offers a detailed understanding of retinal microvascular alterations, utilizing metrics like vessel density and choriocapillaris flow deficits. This chapter emphasizes the predictive value of these biomarkers, highlighting their role in early detection, precise monitoring, and selecting appropriate therapeutic strategies. By integrating OCT and OCTA, clinicians can enhance visual outcomes and optimize the management of DR and DME.

Keywords: diabetic retinopathy, diabetic macular edema, optical coherence tomography, optical coherence tomography angiography, biomarkers

1. Introduction

Diabetes mellitus (DM), a disease marked by elevated blood glucose levels due to metabolic dysfunction, affects 537 million adults aged 20–79 years globally, a figure projected to rise to 643 million by 2030 and 783 million by 2045 [1]. Diabetic retinopathy (DR), a vascular complication of DM, is the leading cause of blindness among adults of working age. A recent meta-analysis revealed a global prevalence of 22.27% for DR, 6.17% for vision-threatening DR, and 4.07% for clinically significant diabetic macular edema (CS-DME) among diabetic individuals [2].

The pathophysiology of DR involves capillary endothelial cell proliferation, basement membrane thickening, and pericyte loss, leading to microaneurysms (MAs), increased vessel permeability, blood-retinal barrier (BRB) destruction, and neurodegeneration due to chronic hyperglycemia [3]. This results in diabetic macular edema

(DME), the primary cause of vision loss among diabetic patients. Without treatment, about 50% of DME patients lose more than two lines of visual acuity (VA) within two years [4]. In advanced stages, capillary blockage and ischemia lead to new blood vessel formation, resulting in proliferative diabetic retinopathy (PDR).

Clinically, DR is identified by the presence of MAs, intraretinal hemorrhages, cotton wool spots, and venous beading. Advanced stages may exhibit neovascularization (NV), vitreous hemorrhage (VH), and tractional retinal detachment (TRD). Diagnostic modalities for detecting DR include fundus fluorescein angiography (FFA), which is essential for visualizing retinal microvascular abnormalities, NVs, and areas of retinal non-perfusion. Fundus autofluorescence (FAF) aids in diagnosing DR by detecting changes in the retinal pigment epithelium (RPE) and providing information on metabolic stress within the retina. Ultra-widefield (UWF) imaging captures a comprehensive view of the peripheral retina, detecting lesions that conventional methods might miss. However, in contemporary practice, Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA) play a more significant role in the screening and diagnosis of DR, offering high-resolution images and detailed views of retinochoroidal vasculature without any dye injection [5].

OCT has become essential in assessing DR due to its non-invasive, reproducible, high-resolution, cross-sectional retinal imaging capability. It does not require skilled operation or pupil dilation and can detect subtle retinal changes not visible during clinical examination [6]. OCT is valuable for both the quantitative and qualitative assessment of structural changes in DR, specifically DME. Various imaging biomarkers have been identified to determine severity, prognosticate, assess treatment response, and detect disease recurrence [7–9].

OCTA is an advanced imaging modality that provides detailed visualization of the retinochoroidal circulation. It separates capillaries at three different levels, identifying MAs, capillary non-perfusion areas (NPAs), and neovascularization before they are clinically apparent [10]. Morphological and qualitative assessment of vascular changes via OCTA aids in understanding the pathophysiological processes, treatment, and follow-up of DR.

This chapter will discuss OCT and OCTA-related biomarkers in the diagnosis, treatment, and prognosis of DR.

2. OCT biomarkers of diabetic retinopathy

2.1 Retinal biomarkers

2.1.1 Retinal thickness

In DME, increased retinal thickness can be present secondary to a breakdown of the BRB and extravasation of fluid into and beneath the retina. The most common terms indicating retinal thickness measurements in OCT are given in **Table 1**.

Numerous studies have examined retinal thickness measurements using OCT. Markan et al. [11] showed that central subfield thickness (CST) might not be reliable for prognosis in DR patients, as the location, extent, and pattern of DME, along with other OCT-related parameters, should be considered. Contrarily, Saxena et al. [12] identified three OCT biomarkers, mean CST, cube volume (CV), and central area thickness (CAT), as valid diagnostic and predictive factors for DME. Their study

Retinal thickness	Definition
Central retinal thickness (CRT) / Central subfield thickness (CST)	The mean retinal thickness within the circular field of 1-mm diameter surrounding the foveola
Central foveal thickness (CFT) / Center point thickness (CPT)	The retinal thickness at the intersection of the six radial OCT scans
Macular volume (MV)	The sum of all volumes of all nine sections defined by the ETDRS grid
Cube average thickness (CAT)	The average thickness for the tissue layers between ILM and RPE over the entire 6 x 6 mm square area
Cube volume (CV)	The average volume of the tissue layers between ILM and RPE over the entire 6 x 6 mm square area

ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

Table 1.
Definitions of retinal thickness measurements in optical coherence tomography.

found that significant increases in CST, CAT, and CV were correlated with the severity of DR. Despite these controversial results, failure to achieve a CST of <300 µm or a reduction of ≤10% in CST is generally seen as a suboptimal anatomical response to anti-vascular endothelial growth factor (anti-VEGF) therapy [13, 14].

Although retinal thickness is a major follow-up criterion in most of the studies, evidence has shown differing correlation between retinal thickness values and both initial and final VA. A subanalysis of the Study of Ranibizumab Injection in Subjects with CD-DME with Center Involvement Secondary to DM (RIDE and RISE) trials revealed that patients with non-significant changes in central foveal thickness (CFT) after anti-VEGF therapy showed similar VA gains and DR improvement as those with early retinal thinning [14]. Similarly, in the Protocol T study, people with 20/40 or better vision who were given bevacizumab (BVZ) treatment had the same functional improvements as those who were given other anti-VEGF drugs, even though they had thicker retina [15]. The study also indicated that while a single CST measurement might modestly correlate with VA, CST fluctuation between visits could be a prognostic indicator. On the other hand, Zhang et al. [7] used machine learning to predict DME patient outcomes after anti-VEGF treatment, identifying CST as a critical predictive factor for VA prognosis. The reason for these contradictory results could be due to the fact that edema can stretch the retina beyond its capacity, causing damage to bipolar axons and permanent changes to the RPE. This, in turn, can lead to VA recovery that does not align with edema resolution. Also, a decrease in CST is not always desirable, as central foveal atrophy, defined as CST below 200 µm, can occur in about 4% of treated DR eyes. In a study by Karst et al. [16], the patients who developed atrophy initially had higher CST and lower VA and received both intravitreal injections and laser treatments for DME.

Macular volume (MV), though strongly correlated with CST, is unlikely to be a reliable prognostic marker due to conflicting results of its relationship with vision in eyes with DRP. Hannouche et al. [17] found that MV is correlated with VA, while Maheswary et al. [18] found no significant correlation. The poor correlation between MV and VA may be due to MV considering extra-foveal thickness, whereas VA reflects foveal function.

2.1.2 Intraretinal cystoid spaces

Intraretinal cystoid spaces (ICS) around the fovea stem from inner BRB disruption due to elevated VEGF levels and Müller cell dysfunction. The prognostic significance of ICS depends on their location, size, and the presence of hyperreflective material within. ICS are classified as small ($<100\text{ }\mu\text{m}$), large (101–200 μm), and giant ($>200\text{ }\mu\text{m}$) according to their size. Larger cysts are shown to be related to macular ischemia, which is an unfavorable prognostic factor for VA [19]. Large as well as giant intraretinal cysts may lead to irreversible visual loss by affecting the outer nuclear layer (ONL) and damage the inner segment/outer segment (IS/OS) junction. In long-standing cases, large coalescent macrocysts may indicate retinal cystoid degeneration (RCD), an end-stage result linked with Müller cell dysfunction or death [20]. A representative OCT image of a large retinal cyst is shown in **Figure 1**.

VEGF levels are crucial in ICS formation, and anti-VEGF therapy effectively reduces vessel permeability and ICS size and number. The location and size of ICS, as well as presence of hyperreflective material—likely fibrin and inflammatory by-products—within the cysts correlate with baseline VA, and improvement in macular anatomy as well as function during intravitreal anti-VEGF therapy [21]. ICS in the inner nuclear layer (INL) respond better to anti-VEGF or corticosteroids than those in the ONL. The inflammatory nature of ICS involves cytokines like Intercellular adhesion molecule 1 (ICAM-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), and Monocyte chemoattractant protein-1 (MCP-1) [22]. Improvement in ICS after dexamethasone (DEX) implant, related to inflammation reduction, has been reported in previous studies [9, 23].

2.1.3 Subretinal fluid

Subretinal fluid (SRF), resulting from outer retinal layer disruption and RPE dysfunction, leads to extracellular fluid accumulation. SRF is generally considered associated with worse VA than ICS at baseline. Although SRF usually responds quickly to treatment in DME cases, it is generally indicative of more severe disease [24].

There are contradictory results about the significance of SRF in DR. A recent study by Park et al. [25] found that the baseline SRF is both a valuable marker for a greater reduction in CST and an indicator of improvement in VA in DME cases. In the post hoc analysis of the Bevacizumab and Ranibizumab in Diabetic Macular Edema (BRDME) trial, eyes with SRF exhibited greater letter gains at 6 months compared

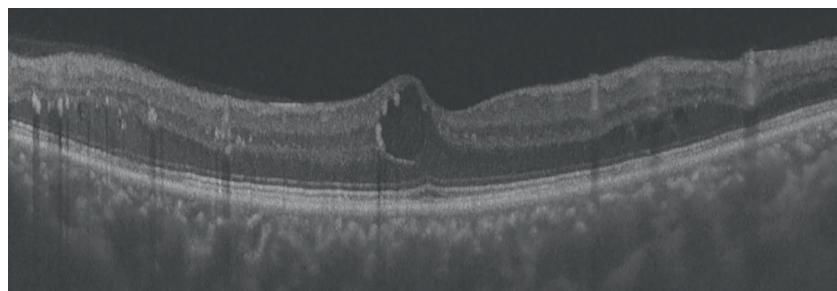


Figure 1.

The presence of a central large retinal cyst with hyperreflective retinal foci on its wall (Courtesy of Mahmut Kaya, MD).

to eyes without SRF, despite no significant difference in the reduction of CST [26]. On the other hand, in the Study of Intravitreal Aflibercept Injection in Patients With DME (VISTA) and Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID) studies, although patients with baseline SRF had a greater treatment effect from aflibercept (AFL), SRF status did not significantly impact overall treatment outcomes with AFL [27]. In the Diabetic Retinopathy Clinical Research Network (DRCR) Protocol T, eyes with centrally located fluid had a mean of 23- μ m greater reduction in CST, although no significant VA change was observed [28]. The morphology of retina in terms of edema type may affect the visual and anatomical results. The cystoid macular edema (CME) morphology was found to be favorable in achieving at least a 20% reduction in CST, followed by serous retinal detachment (SRD) and diffuse retinal thickening (DRT) in eyes treated with ranibizumab (RBZ) or AFL; however, morphology was not associated with visual outcome [29]. Similarly, a retrospective study reported that the CME subtype showed the greatest improvement in VA and reduction in CST in eyes treated with intravitreal triamcinolone acetonide (TA) compared to DRT and SRD subtypes [30].

The exact reasons for the association between SRF and improved outcomes are unclear. One hypothesis is that SRF acts as a physical barrier, protecting retinal structures from further damage. Additionally, SRF may contain protective substances, with anti-VEGF injections enhancing this effect. This is supported by studies indicating that eyes with SRF have a lower risk of developing geographic atrophy (GA) [31].

2.1.4 Disorganization of the retinal inner layers

Disorganization of the retinal inner layers (DRIL) is marked by the loss of clear boundaries between the ganglion cell complex (GCC), INL, and outer plexiform layer (OPL). This novel biomarker appears in various retinal diseases as a response to retinal stress and may represent disruptions in the neural transmission pathway involving bipolar, amacrine, and horizontal cells [32]. These disruptions impair the transmission of visual signals from photoreceptors to ganglion cells and the nerve fiber layer. Therefore, it's not surprising that DRIL has been associated with abnormalities in multiple measures of visual function, such as VA, contrast sensitivity, multifocal electroretinography (mfERG), and standard automated perimetry (SAP), even in the absence of DME [32, 33].

The exact pathophysiology of DRIL remains unclear, but it is proposed that mechanical stretching of bipolar axons due to chronic retinal thickening may cause damage, as Pelosini et al. [34] found that the neurosensory retina (NSR) has a degree of elasticity that if exceeded, leads to snapping of bipolar neurons. Also, macular ischemia may contribute to DRIL formation, as studies have found a correlation between DRIL and capillary non-perfusion on both FFA and OCTA [35].

DRIL is more frequently identified in eyes with increasing DR severity and is associated with worse visual outcomes. It is more likely to occur in mild to moderate non-proliferative diabetic retinopathy (NPDR) compared to diabetic patients without retinopathy, with the risk increasing with the duration of diabetes [32]. According to the study by Nadri et al. [36], there was a significant positive correlation between DRIL and CAT, CST, and the level of ellipsoid zone (EZ) disruption, while there was a negative correlation between DRIL and retinal nerve fiber layer (RNFL) thickness. Correlation has also been made between DRIL and other OCT findings, including enlargement of the FAZ and disruption of the external limiting membrane (ELM) [37, 38]. Moreover, DRIL can have a VA-predictive value independent of macular thickness [29, 39].

The change in DRIL extent is an important predictor of vision change after intravitreal anti-VEGF and steroid treatment. A greater baseline DRIL extent in the 1-mm foveal area and an early worsening in DRIL were predictive of worse VA at long-term follow-up after anti-VEGF treatment [40]. In a study by Vujosevic et al. [41] comparing the response of OCT signs to RBZ and DEX implant in eyes with DME, a greater reduction in DRIL extent was observed in eyes treated with DEX implant. Several other studies also reported better outcomes with steroid and proposed that in case DRIL does not adequately improve, an early switch from anti-VEGF treatment to intravitreal steroids may be preferred [29, 42]. These observations may be explained by the neuroprotective effect of corticosteroids, as they may promote neuronal survival via Müller cells and by suppressing microglial reactivity. **Figure 2** shows the presence of disorganization of the retinal inner layers in a patient with DR, which is observed during the first week of anti-VEGF treatment.

2.1.5 Hyperreflective retinal foci

Hyperreflective foci (HFs) in DME are small, well-circumscribed dots not visible on biomicroscopy or fundus photography, often appearing before clinically detectable DR or DME [43]. HF is not specific to DR; it is also observed in conditions like age-related macular degeneration, central serous chorioretinopathy (CSC), retinal vein occlusions (RVOs), and Coats disease, and occasionally in normal individuals [44]. Initially, HF is detected in the inner retinal layers on OCT and may later move to the outer layers. Vujosevic et al. [43] identified three types of HFs based on the appearance and location:

- HF $\leq 30 \mu\text{m}$ in diameter, reflecting like the nerve fiber layer and located in both the inner and outer retina, likely represents activated microglial cells
- HF $> 30 \mu\text{m}$ in diameter, reflecting like the RPE-Bruch membrane complex with back shadowing, located in the outer retina, likely represents hard exudates
- HF $> 30 \mu\text{m}$ in diameter, similar reflectivity to the RPE-Bruch membrane complex with back shadowing, located in the inner retina, may indicate MAs.

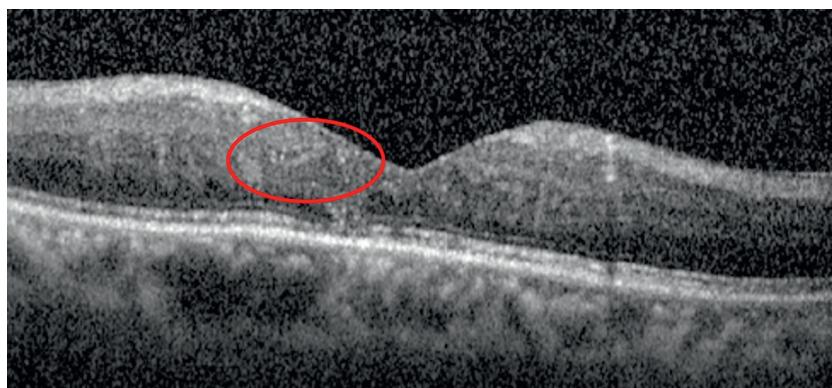


Figure 2.
The presence of disorganization of the retinal inner layers (red circle).

Initial descriptions suggested that HFs could be lipid-laden macrophages or extravasated lipoproteins, early indicators of subclinical BRB breakdown, but later evidence proposed that HFs could be markers of chronic inflammation and activated microglia in DR [45]. A significant correlation between small HF numbers and subclinical neurodegeneration supports the inflammatory hypothesis [46].

Studies show that DEX implants reduce HFs more effectively than anti-VEGF treatments, though some studies found similar reductions with both treatments [47, 48]. While some studies found a correlation between HF and better VA after treatment, others show no such association or even poorer outcomes [49, 50].

2.1.6 Pearl necklace sign

First defined by Gelman et al. [51], the pearl necklace sign refers to HF forming a continuous ring around the inner wall of cystoid spaces in the retina. These dots often become hard exudates as the edema resolves, suggesting the pearl necklace sign is a precursor to hard exudates. Generally, the presence of this sign does not affect the visual prognosis or the response to intravitreal treatment, except when located subfoveally. In such cases, irreversible photoreceptor damage can lead to poor visual outcomes [52]. **Figure 3** shows the presence of a pearl necklace sign in a patient with poorly controlled DM.

2.1.7 Bridging retinal processes

Bridging retinal processes are vertical remnants of neuroretinal tissue, primarily composed of Müller and bipolar cells, stretched between cystic cavities, connecting the inner and outer retinal layers. Their presence helps in transmitting visual impulses to the optic nerve axons; therefore, it is associated with better visual outcomes post-treatment, serving as a reliable biomarker for visual prognosis. Moreover, Markan et al. [11] showed that the lack of bridging processes leads to retinal thinning and atrophy. **Figure 4** illustrates the presence of bridging retinal processes.

2.1.8 Integrity of external retina

The cone outer segment tip (COST), also known as the interdigitation zone (IZ), appears as a hyperreflective band between the EZ and RPE on OCT. It is a marker of

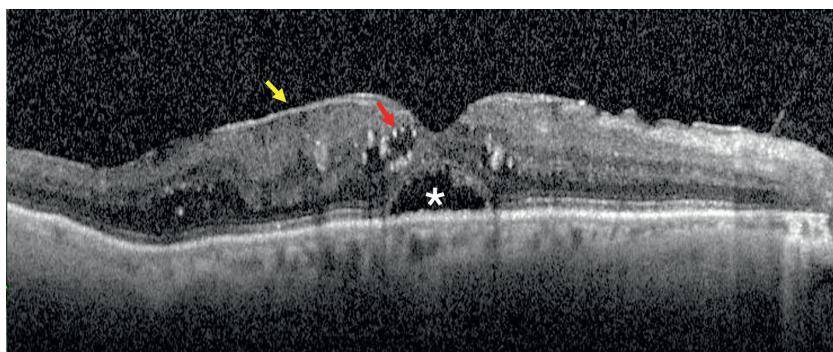


Figure 3.
The presence of pearl necklace sign (red arrow), epiretinal membrane (yellow arrow), and subretinal fluid (white asterisk) in a patient with poorly controlled DM.

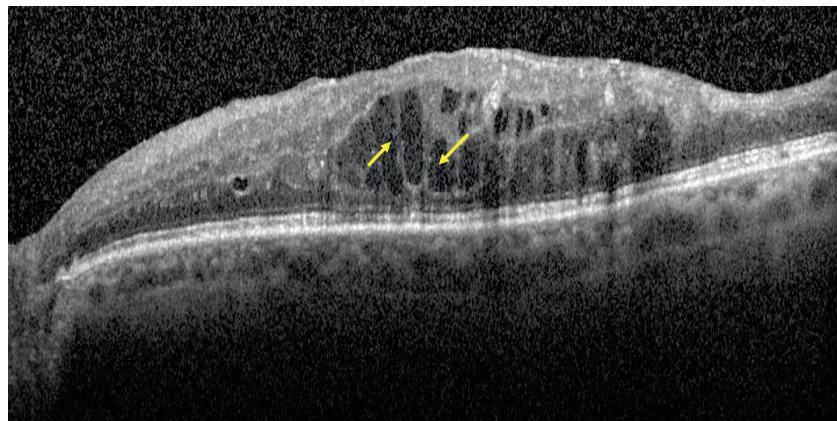


Figure 4.
The bridging retinal processes (yellow arrows) between intraretinal cystic cavities.

photoreceptor integrity. The EZ, previously termed the inner segment/outer segment (IS/OS) junction, represents the photoreceptors' mitochondria-rich zone, essential for their high-energy consumption. The ELM comprises zonula adherens connecting photoreceptor inner segments and Müller cell apical processes, acting as a barrier for macromolecule movement between these cells. In diabetic eyes, elevated VEGF levels can decrease occludin, a tight junction protein, compromising the ELM's barrier and increasing vascular permeability [53]. The mechanism of photoreceptor dysfunction in DME is multifactorial and involves impaired energy metabolism, inflammation, and microvascular ischemia [54].

Damage or disruption of photoreceptors is commonly visualized on OCT as a loss of integrity in the ELM, EZ, and IZ bands. Although the correlation between photoreceptor damage stages and OCT findings is not yet clearly established histopathologically, OCT studies of retinal degenerative diseases show that the lengths of the ELM, EZ, and IZ bands are highly correlated [55]. Disorganization appears to occur sequentially: first in the IZ, then in the EZ, and finally in the ELM. Qualitatively, each outer retinal layer is classified as absent (not visible), disrupted (partially visible), or intact (fully visible) in the foveal region [20]. A more recent approach involves a quantitative assessment of the EZ's relative intensity. This method expresses the EZ's relative intensity as a ratio compared to the ELM on OCT [56]. On the other hand, Borrelli et al. [57] developed an algorithm using the vitreous and RNFL intensities as references to normalize EZ intensity to better evaluate its status. The photoreceptor outer segment (PROS) is defined as the distance between the RPE and the junction of the photoreceptor IS/OS. In patients with DR, the PROS length is shorter compared to those without DR and correlates better with VA than macular thickness, serving as a more reliable prognostic marker [58].

Achiron et al. [59] first reported the association between treatment and EZ/COST integrity, demonstrating that the recovery of EZ/COST defects correlated with VA improvement following intravitreal BVZ injections in treatment-naïve DME patients over a 3-month follow-up. Similarly, Serizawa et al. [60] found that in 41 DME eyes treated with laser therapy, anti-VEGF, and/or vitrectomy, the restoration of retinal outer layers, especially the COST, was a sensitive marker of treatment outcome. On the other hand, Koc et al. [61] proposed that EZ and ELM integrity may be more reliable than COST, as COST fragmentation artifacts are not uncommon in healthy eyes. Longitudinal studies show that disrupted foveal EZ, ELM, and COST predict worse

subsequent VA and less VA gain in eyes treated with anti-VEGF and DEX implants, with this association observable up to 24 months [29, 62]. Post hoc analysis of the VISTA study showed that AFL treatment improved EZ integrity, which was maintained through week 100 follow-up [63].

2.1.9 Retinal pigment epithelium thickness

RPE thickness is a biomarker for predicting the functionality of the outer BRB. Eyes with PDR and DME exhibit decreased RPE thickness, indicating degenerative changes, likely due to ischemia disrupting the RPE-photoreceptor complex [64]. Boynton et al. [65] found that untreated patients with PDR had diffusely thinned RPE layers compared with healthy controls. On the other hand, Tavares Ferreira et al. [66] reported no significant change of RPE in subjects with or without diabetes.

2.1.10 Foveal eversion

A completely convex central fovea, known as foveal eversion, is linked to a higher rate of persistent DME compared to a normal foveal profile, regardless of treatment with intravitreal anti-VEGF or corticosteroids. It is also associated with higher retreatment rates in eyes treated with intravitreal steroids and a higher frequency of persistent DME. The underlying cause may involve Müller cell impairment, although the precise mechanism is not yet understood [67].

Figure 5 illustrates various OCT biomarkers observed in a patient undergoing anti-VEGF therapy.

2.1.11 Parallelism

SD-OCT introduced the parameter “parallelism,” which refers to the integrity of retinal layers and serves as a potential biomarker for predicting visual outcomes in DME [68]. This parameter encompasses the continuity of the ELM, the EZ of the

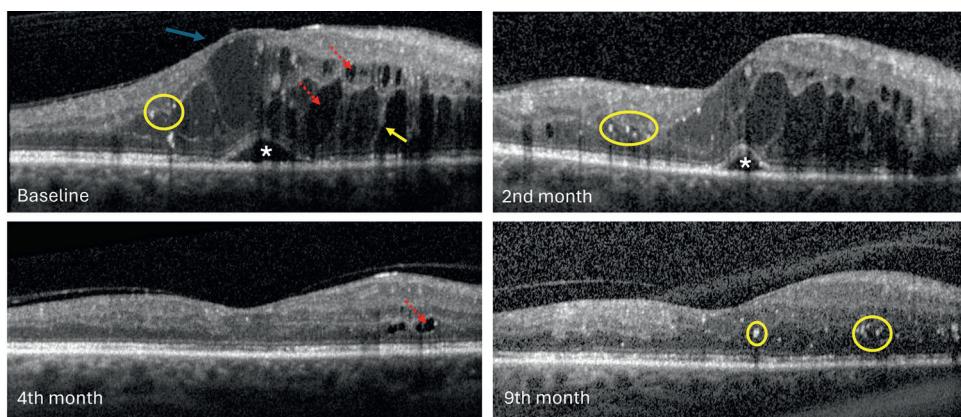


Figure 5.
The initial OCT image displays subretinal fluid (white asterisks), intraretinal cystoid spaces (red dashed arrows), hyperreflective dots (yellow circle), bridging retinal processes (yellow arrow), and foveal eversion (blue arrow). Follow-up OCT images at 2, 4, and 9 months post anti-VEGF treatment show a reduction in retinal thickness and improvement in subretinal fluid and intraretinal cystoid spaces. The 9-month OCT image reveals a few hyperreflective dots and disruption in the integrity of the outer retinal layers. (Courtesy of Taylan Ozturk, MD).

inner segment, as well as the presence of HF in the outer retinal layers. Parallelism is notably reduced in eyes with DME compared to normal eyes and shows a positive correlation with VA. A lack of HF in the outer retinal layers is significantly linked to increased parallelism and improved VA.

2.2 Vitreomacular interface biomarkers

The vitreomacular interface biomarker is crucial in the pathogenesis and progression of DR. Metabolic factors in diabetes can cause early vitreous liquefaction and cross-linking, leading to incomplete posterior vitreous detachment (PVD) and vitreoschisis. This can result in vitreous instability and macular traction. Studies have shown elevated levels of inflammatory and angiogenic factors, such as VEGF, IL-6, IL-8, ICAM-1, and MCP-1, in the vitreous fluid of patients with DME and PDR, implicating these molecules in retinal vascular permeability and macular edema [69].

Early studies, such as those by Nasrallah et al. [70], highlighted the importance of the vitreous in DME. A significant relationship between PVD and the absence of macular edema was found, suggesting that vitreous detachment plays a key role in DME resolution. Further research indicated that spontaneous resolution of macular edema occurred in a higher percentage of eyes with PVD compared to those without PVD. However, in eyes requiring anti-VEGF treatment, those with vitreomacular adhesion (VMA) showed greater VA improvements than those with complete PVD, possibly due to prolonged clearance of anti-VEGF molecules in eyes with VMA [71]. The posterior hyaloid's separation from the macula during PVD formation improves retinal oxygenation and reduces the reservoir of cytokines and angiogenic mediators near the macula.

The posterior hyaloid acts as a scaffold for neovascular growth due to its tight adhesions with retinal blood vessels, while the internal limiting membrane (ILM) supports glial proliferation, contributing to persistent macular edema and recurrent epiretinal membrane (ERM). According to Kang et al. [50], the incidence of new ERM formation is approximately 9.5% in DR. Significant vitreomacular traction (VMT) may necessitate pars plana vitrectomy (PPV) and ERM removal for eyes with suboptimal response to anti-VEGF or DEX implants, as recommended by the European Society of Retina Specialists (EURETINA) guidelines for DME eyes with anteroposterior traction [72]. Vitrectomy has been shown to reduce central subfield thickness and improve VA in such cases. The DRCR Protocol D offered vitrectomy to patients with DME and VMT, achieving a reduction of central subfield thickness to less than 250 µm in almost half of the eyes and a mean gain of 5 letters in visual acuity at 6 months [73]. **Figure 6** shows the thick posterior hyaloid and ERM formation in diabetic eyes.

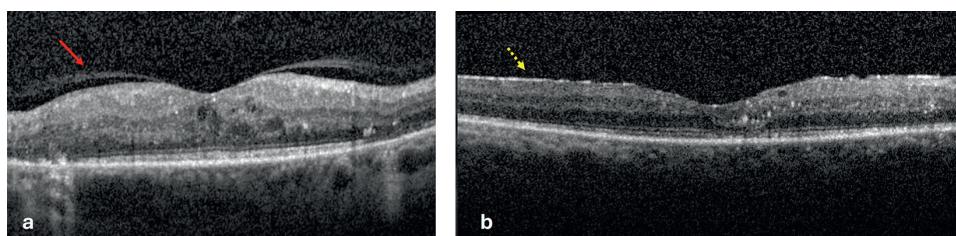


Figure 6.

(a) The presence of a thickened posterior hyaloid (red arrow) and (b) the formation of an epiretinal membrane (yellow dashed arrow) in patients with diabetic retinopathy.

2.3 Choroidal biomarkers

The choroid plays a critical role in supplying blood to the photoreceptor cells and the RPE, receiving approximately 95% of ocular blood flow and serving as the primary source of oxygen and nutrients for the outer retina. The involvement of the choroid in DR was first evidenced through histopathological studies, which revealed increased arteriosclerosis and periodic-acid Schiff (PAS) positive material within the arterial and capillary walls of diabetic eyes [74]. The term “diabetic choroidopathy” was later introduced by Hidayat et al. [75] in 1985, based on their description of histopathological findings in seven enucleated eyes suffering from late complications of diabetes. Choroidal impairment in DR can lead to photoreceptor dysfunction and death, as well as damage to the choriocapillaris (CC), which impairs the clearance of waste products from the RPE cells, resulting in their accumulation at Bruch’s membrane.

The advent of advanced imaging technologies, such as enhanced depth imaging (EDI)-OCT and swept-source (SS)-OCT, has significantly improved the visualization and measurement of the choroidal vasculature. These technologies enable detailed examination of choroidal structure and provide reproducible measurements of choroidal thickness. Recently, investigations have focused on the subfoveal choroidal thickness (SFCT), choroidal vascular index (CVI), and hyperreflective choroidal foci (HCF) as potential biomarkers for DR. These biomarkers offer new insights into the pathophysiology of DR and could contribute to the development of more effective diagnostic and therapeutic strategies.

2.3.1 Subfoveal choroidal thickness

Subfoveal choroidal thickness (SFCT), measured from the outer edge of the RPE to the inner sclera on EDI-OCT, may serve as a potential marker for choroidal vascular-ity. However, there is consensus about the SFCT findings in DR. While some studies found thicker SFCT in diabetic patients compared to controls, regardless of DR or DME severity, others linked thicker SFCT with increased DR severity and DME presence [76]. Conversely, some studies noted reduced SFCT associated with DME and DR severity [77, 78]. The relationship between choroidal thinning and DR is unclear, as it is not known whether choroidal thinning occurs before the onset of DR or is a consequence of DR-related alterations. Choroidal vasculature alterations may precede DR in diabetes [79, 80]. Choroidal thickening in diabetic eyes may result from vascular hyperperme-ability due to elevated nitric oxide (NO) and VEGF levels [81]. SFCT reduction following anti-VEGF therapy supports VEGF’s role in choroidal thickening [82]. These discrepancies between the studies may stem from differences in study design, patient demograph-ics, and racial backgrounds. Various confounding factors, including age, sex, axial length (AL), and treatment history, influence choroidal thickness [83]. Standardizing measure-ment times in future studies is crucial due to significant diurnal variation [84].

The predictive value of SFCT for treatment response in DME is inconclusive. A thicker baseline SFCT was shown to be correlated with favorable functional and anatomical results with DEX implant and anti-VEGF treatment [85]. On the other hand, Campos et al. [86] showed that baseline SFCT decreased with anti-VEGF treat-ment but did not predict DME outcome. Moon et al. [85] reported that greater SFCT reduction with DEX implant was associated with greater VA gain and CST reduction. Several other studies also showed that anti-VEGF and DEX treatments consistently reduce choroidal thickness, though the extent of reduction does not correlate with treatment outcomes [87, 88].

2.3.2 Choroidal vascularity index

Given the numerous confounding factors and diurnal variations affecting SFCT, a reproducible quantitative analysis of choroidal vascularity is necessary. CVI is a newly developed metric in OCT that quantifies the vascular condition of the choroid and has been recently presented as a novel biomarker for monitoring the course of DR [89]. Studies have shown that while choroidal thickness is unaltered in DR, CVI correlates with progressing DR [90]. Comparing diabetic eyes and healthy ones, a study by Keskin et al. [91] found that CVI tends to be lower in diabetic patients with or without DR compared to healthy controls. CVI can be affected by the severity of DR. According to Kim et al. [92], CVI declined as DR advanced to PDR. In the mild/moderate NPDR group, SFCT was higher, and CVI was significantly lower compared to the no DR group. The status of CVI also affects the treatment response, as DME eyes with higher baseline CVI are more likely to achieve at least a 5-letter gain in VA with anti-VEGF treatment [93].

2.3.3 Hyperreflective choroidal foci

Hyperreflective choroidal foci (HCF) are typically dot-like or round, regular lesions in the choroid. According to a study by Roy et al. [94], the first to define HCF, these lesions are likely composed of migrated hyperreflective retinal foci (HRF), as all eyes with HCF also had HRF. In that study, eyes with HCF had significantly worse VA and higher mean CFT compared to those without HCF, indicating that HCF is associated with greater severity of DR and poorer visual outcomes. Another study by Saurabh et al. [95] found that the presence of HCF is associated with poorer initial VA and may also be indicative of worse final visual outcomes. In a retrospective longitudinal study, Szeto et al. [29] found that nearly half of the eyes with baseline HCF experienced a decrease in HCF numbers following treatment, with greater improvements in VA compared to those without a reduction in HCF.

3. OCT angiography biomarkers of diabetic retinopathy

OCTA functions by monitoring the movement of red blood cells (RBCs) over time through volumetric OCT scans. Repeated scans at each B-scan position enable the detection of motion contrast, which corresponds to blood flow, the primary expected motion in retinal vessels [5]. Unlike FFA, OCTA does not reveal vascular leakage. Also, the limited field of view restricts OCTA's utility as a screening tool. On the other hand, it has several advantages, such as being non-invasive, having more rapid data acquisition, and thus facilitating more frequent and faster monitoring. Furthermore, OCTA can generate three-dimensional (3D) images that reveal the depth of structures, allowing for the observation of specific capillary networks. This capability provides important quantitative information about the microvasculature of the retina. Enhanced software algorithms generate images of the superficial capillary plexus (SCP) and deep capillary plexus (DCP), and users can further refine segmentation to visualize additional layers, such as the intermediate capillary plexuses (ICPs), thus revealing pathologies not detectable with traditional dye-based angiography.

Various OCTA scan protocols cater to different clinical and research needs, utilizing a consistent 304×304 B-scan framework. The 3×3 mm scan, due to its increased density in comparison to the 6×6 mm and 12×12 mm scans, provides enhanced

resolution, leading to a more accurate identification of findings. Hirano et al. [96] conducted a study in which they analyzed three different scan sizes (3×3 mm, 6×6 mm, and 12×12 mm) to compare retinal parameters between patients with DR and individuals without the disease. DR patients exhibited markedly reduced perfusion density (PD), vascular length density (VLD), and fractal dimensions (FDs) across all scan sizes and retinal layers. The swept source (SS)-OCTA images, sized 3×3 mm, clearly showed notable variations in these measurements between NPDR eyes with and without DME in the deeper layers of the retina. The discrepancies were not detected in the 6×6 mm and 12×12 mm SS-OCTA images. Another study comparing 3×3 mm and 6×6 mm OCTA scans for evaluating NPDR found that 3×3 mm scans better delineated the FAZ and detected vascular remodeling due to higher scan density [97]. Conversely, 6×6 mm scans were more sensitive in detecting MAs due to their larger scan area (**Table 2**).

3.1 Foveal avascular zone

The human foveola, characterized by its absence of rods and maximum density of cone photoreceptors, is crucial for central vision. This region, known as foveal avascular zone (FAZ), lacks vasculature and overlying inner retinal tissue, which minimizes light scattering and enhances optical quality. In healthy eyes, the FAZ area varies widely, ranging from 0.071 mm^2 to 0.527 mm^2 [98].

In DR, the FAZ is shown to be enlarged due to capillary loss in adjacent vessels, with a larger FAZ linked to thinner SFCT, lower body mass index (BMI), shorter AL, and more severe DR [99]. In addition to the FAZ area, metrics, such as FAZ perimetry, radius, and circularity, are employed for the evaluation of FAZ. FAZ circularity,

OCTA metric	Description
Foveal Avascular Zone (FAZ) area	Measurement of the FAZ size in mm^2
Foveal Avascular Zone (FAZ) circularity	A quantitative representation of the extent to which the FAZ resembles a perfect circle
Non-perfusion Area (NPA)	Area of absent blood flow
Vessel Density (VD)	Total area of perfused vasculature per unit area indicating the extent of blood flow within a given area. Similar to perfusion density
Vessel Length Density (VLD)	Percentage of the total vascular length divided by the total area
Vessel Skeleton Density (VSD)	Density of binarized vessel network evaluating the density of the simplified, skeletonized representation of the vessel network
Vessel Diameter Index (VDI)	The average vessel caliber of blood vessels is represented by the area occupied by a blood vessel from the binarized picture throughout the entire length of the vessel from the skeletonized image
Fractal Dimensions (FDs)	A mathematical parameter used to describe the complexity of blood vessels
Intercapillary Spaces	Space between adjacent capillaries

Table 2.

The detailed explanation of the metrics used in Optical Coherence Tomography Angiography for evaluating retinal vascular health.

which refers to its similarity to a perfect circle, can provide more informative insights into disease-induced microvascular changes compared to merely considering the FAZ area. Obstruction of the innermost capillaries around the fovea causes the FAZ to become irregular, making FAZ circularity a marker for capillary dropout and macular ischemia. A study by Tang et al. [99] found that worsening DR is significantly associated with an enlarged FAZ area, decreased FAZ circularity, lower vessel density (VD), and reduced FD in the SCP, as well as an enlarged FAZ area and lower VD in the DCP. A larger FAZ correlates with the presence of DRIL and poorer visual outcomes [100]. Furthermore, abnormalities in the FAZ have been observed in diabetic patients without clinical DR. De Carlo et al. [101] demonstrated significant FAZ enlargement in these patients compared to non-diabetic individuals. Nevertheless, the evidence remains equivocal, since several studies validate the FAZ enlargement as a biomarker in DR, while others indicate no significant correlation between FAZ and the severity of DR [102, 103]. **Figure 7** shows the enlarged FAZ area with decreased FAZ circularity as well as presence of MAs.

3.2 Non-perfusion areas

Non-perfusion areas (NPAs) are markers of vascular damage and retinal ischemia, and although not currently included in the grading of DR, they hold predictive potential for the progression from NPDR to PDR [104]. As DR advances, the extent of NPA increases. OCTA appears to outperform FFA in visualization of these regions, frequently detecting non-perfusion in areas that FFA identifies as perfused, probably attributed to slow blood flow.

NPA in all three retinal plexuses, including SCP, ICP, and DCP, has a correlation with intraretinal microvascular abnormalities (IRMAs) and neovascularization [105]. A study involving 122 individuals with NPDR from type 2 DM (T2DM) found

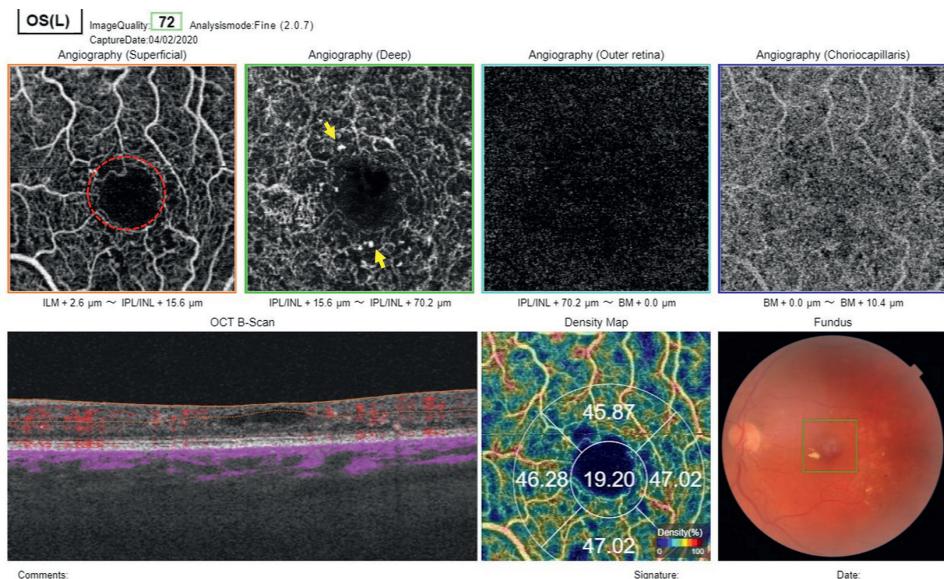


Figure 7.
Enlarged FAZ area with decreased FAZ circularity (red dashed circle) and the presence of MAs (yellow arrows) (Courtesy of Ali Osman Saatci, MD).

a significant association between retinal neurodegeneration, thinning of the retinal GCC, and increased retinal NPA [106]. This highlights the clinical value of NPA as a marker for tracking DR progression.

3.3 Vessel density

Vessel density (VD) is a measure of retinal microvasculature perfusion, calculated by dividing the area of blood vessels by the total measured area in binarized images. VD is influenced by age, gender, retinal layer thickness, and is highly correlated with signal strength [107, 108].

Notably, diabetic patients without DR exhibit a decrease in VD in both SCP and the DCP. Santos et al. [109] reported that eyes with preclinical retinopathy show early retinal capillary closure, predominantly within the SCP, resulting in decreased VD. These findings suggest that initial retinal microvascular changes in type 2 DM are characterized by capillary closure or reduced blood flow, primarily within the SCP, corroborating the results of de Carlo et al. [101]. Conversely, some studies emphasize a significant decrease in VD in the DCP more than in the SCP. Veiby et al. [110] found that lower VD in the DCP was the only significant OCTA factor associated with the progression of NPDR. The susceptibility of DCP to ischemic damage, due to its location in a watershed zone adjacent to the high oxygen demands of the OPL, is supported by histologic studies indicating its vulnerability to injury [111]. Tang et al. [99] observed that lower VD was associated with shorter AL, worse VA, and more severe DR, with decreased VD in the DCP correlating with VA deterioration, implying that DCP VD reflects capillary loss in patients with DME. Additionally, the ICP VD and flow index decrease, and the area of non-perfusion increases with DR progression, paralleling changes in the DCP [112].

The extent of DCP loss and OPL disruption in DME can predict responsiveness to anti-VEGF treatment, with decreased VD in the DCP indicating worse VA and reflecting capillary loss in patients with visual impairment due to DME [113].

3.4 Choriocapillaris

Choroidal circulation supplies oxygen and nutrients crucial for the choroid and outer retina. Traditional dye-based angiography has limitations in measuring choroidal blood flow. OCTA offers promise in visualizing and quantifying choroidal vasculature, particularly the CC. Nevertheless, commercial OCTA systems frequently do not possess adequate resolution to quantify the highly packed CC in the posterior pole, where the distances between capillaries (5–20 μm) are greater than the lateral resolution of OCT (15–20 μm). To address this, researchers propose using flow deficit analysis to assess CC perfusion, where flow deficits indicate areas with inadequate or below-detectable CC flow by OCT systems [114]. Studies, such as by Dai et al. [103], have noted increased CC flow deficits in diabetic eyes without retinopathy compared to age-matched healthy controls. This reduction in CC flow may precede macular flow changes, suggesting it could serve as an early marker for microvascular dysfunction in diabetes. Histopathological studies have similarly observed more pronounced CC dropouts postmortem in diabetic individuals compared to non-diabetic subjects [115].

3.5 Vessel length density

Vessel length density (VLD), also known as skeleton density (SD), enhances VD by quantifying the total length of vessels without regard to their diameters [116].

Unlike VD, which assesses vessel presence per unit area, VLD assigns equal weight to large vessels and small capillaries, each represented as single-pixel lines. Therefore, VLD is particularly sensitive to changes in capillary-level perfusion compared to VD. Therefore, VLD is considered a more refined metric for evaluating microvascular perfusion dynamics [96].

3.6 Vessel tortuosity

Retinal vessel tortuosity quantifies the curvature integral normalized by the vessel's total path length. Initially assessed via computer-assisted programs on fundus photographs, increased vessel tortuosity has been observed in diabetic patients compared to healthy controls [117].

3.7 Microaneurysms, intraretinal microvascular abnormalities, and neovascularization

Microaneurysms, clinically identified as deep-red dots ranging from 25 to 100 μm in diameter on ophthalmoscopy, are often the earliest visible signs of DR. Studies have linked increased MA count and turnover with higher risks of DR progression and DME [118]. Using OCTA, Thompson et al. [119] demonstrated superior detection of MAs compared to dilated clinical examination alone, highlighting OCTA's depth-resolved capability in precisely localizing these lesions. However, OCTA may not detect all MAs seen on FFA, possibly due to slow blood flow rates or turbulence within MAs [120]. Parravano et al. [121] integrated OCT and OCTA parameters to study MA progression and its impact on retinal extracellular fluid accumulation over one year in NPDR patients. They found that hyperreflective MAs at baseline were significantly associated with increased fluid accumulation, emphasizing OCTA's potential for predicting disease progression and guiding treatment timing in DME. Studies, including those by Park et al. [122], have identified MAs across all retinal plexuses, with a predilection for originating from the DCP over the SCP. This suggests that initial DR changes may originate more frequently from the DCP [121].

In severe NPDR, IRMA is a hallmark according to the Early Treatment Diabetic Retinopathy Study (ETDRS). OCTA, combined with conventional OCT B-scan, provides both en face and cross-sectional views, aiding in the differentiation of IRMA from NV [123]. IRMAs appear on OCTA as anomalous, branched, dilated retinal vessels that remain confined within the retina without protruding into the vitreous [124]. On the other hand, NV typically shows supraretinal flow crossing membranes and extending into the posterior hyaloid, thereby enhancing diagnostic accuracy. Recent studies demonstrate OCTA's capability to detect early NVs, classify lesions, and understand their morphological patterns in PDR [123, 125]. Longitudinal studies using OCTA, such as by Motulsky et al. [126], monitor NV progression and treatment response in PDR, noting decreased flow within NV post-treatment with anti-VEGF and/or panretinal photocoagulation (PRP). Comparisons with FFA, as seen in a study by Russell et al. [127], reveal OCTA's superior visualization of NV dynamics pre- and post-PRP treatment [128, 129]. These findings suggest OCTA could become the primary imaging tool for managing NV in PDR, showcasing its potential in assessing treatment outcomes following PRP. **Figure 8** presents an OCTA image of the optic disk, revealing severe NV in a patient with PDR.

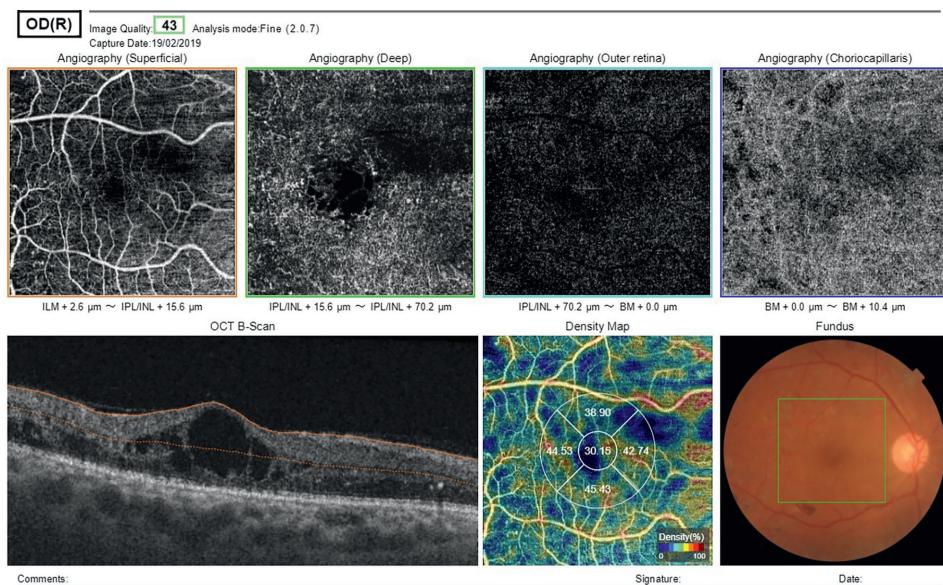


Figure 8.
OCTA image of the optic disk in a patient with PDR demonstrating the presence of an extensive NV (Courtesy of Ali Osman Saatci, MD).

3.8 Fractal dimension and lacunarity

Fractal dimension (FD) quantifies vascular complexity by analyzing skeletonized images through the box-counting method. Studies by Bhardwaj et al. [130] and Kim et al. [131] reveal significantly lower FD values in DR eyes compared to healthy controls, particularly in the SCP, with FD decreasing as DR severity worsens. Serra et al. [132] demonstrate that eyes with peripheral NPAs exhibit lower FD and higher lacunarity (LAC) in both SCP and DCP, correlating with the extent of NPAs.

Reduced FD values are associated with increased LAC, suggesting compromised perfusion in the peripheral retina. This condition may contribute to diabetic microangiopathy, promoting NPAs and triggering inflammatory responses via cytokine release and VEGF activity. Higher LAC values indicate larger and more irregularly distributed lacunae, characteristic of severe DME observed on OCTA [133]. Fan et al. [134] found that FD of the entire retina correlates strongly with the extent of peripheral retinal ischemia in DR. These findings underscore the utility of fractal analysis in objectively assessing microvascular changes and their systemic implications in diabetic retinal diseases.

3.9 Intercapillary spacing

Intercapillary spacing has emerged as a sensitive indicator for early capillary dropouts and ischemic regions in DR. Bhanushali et al. [135] showed intercapillary spacing as more sensitive parameter than VD and FAZ to detect NPA. Mendes et al. [136] demonstrated that abnormal intercapillary spaces effectively distinguished eyes with DR from controls across different ETDRS severity stages. However, the reliability of this metric is influenced by the quality of binarized en face slab images, exhibiting greater variability compared to measures such as VD and FAZ.

3.10 Suspended scattering particles in motion

Suspended scattering particles in motion (SSPiM) are OCTA detected signals found within retinal fluid pockets near vascular-avascular junctions, predominantly in the Henle fiber layer [137]. These signals are not exclusive to DME but are also present in other exudative maculopathies. Their formation is attributed to extravasated lipids, and their presence may decrease as hard exudates develop in some patients [138].

3.11 Diabetic macular edema

OCTA metrics associated with DME include lower VD in the SCP, diminished perfusion in the DCP, increased flow deficit in the CC, as well as altered FAZ characteristics, such as increased area and decreased circularity [139]. ICS, visualized as round black flow voids on OCTA, are more prominent in the DCP than in the SCP. These cystic areas, often surrounded by NPA in chronic DME, suggest underlying ischemia preceding the development of edema. MAs within the DCP are also implicated in DME pathogenesis [140]. OCTA-based biomarkers, including FAZ dimensions and VD across multiple capillary plexuses, aid in diagnosis, prognosis, and monitoring of VA in response to treatment. Studies indicate that a higher number of MAs within the DCP and a larger FAZ area correlate with poorer response to anti-VEGF treatment in DME cases [141].

OCTA has practical limitations in evaluating DME, such as segmentation errors due to retinal edema and signal intensity reduction due to fluid accumulation in deeper retinal layers [142]. Furthermore, discrepancies between OCTA flow voids and actual cystic spaces are noted, as fluid may compress vessels, reducing flow below

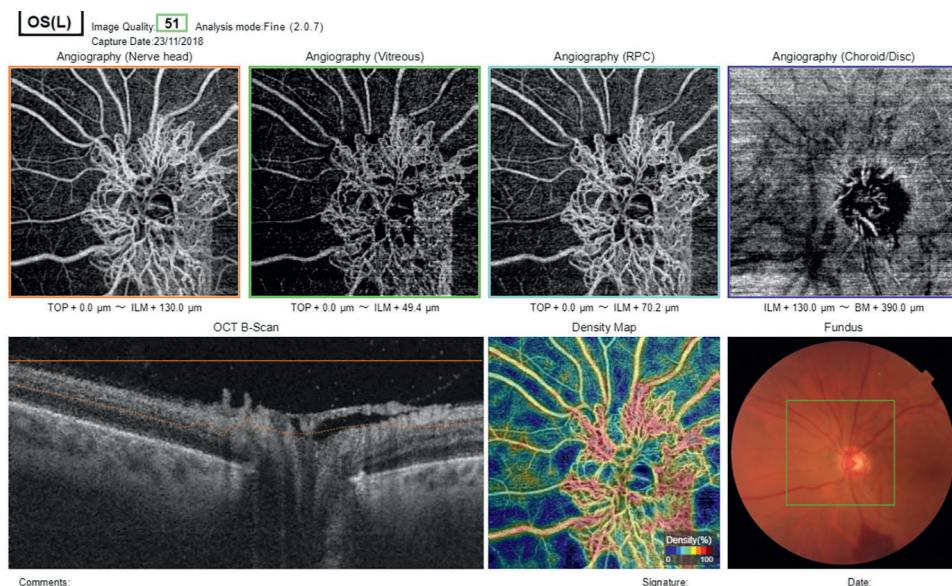


Figure 9.

OCTA image of a patient with severe diabetic macular edema (DME) showing intraretinal cysts (ICS) in both the superficial capillary plexus (SCP) and the deep capillary plexus (DCP) (Courtesy of Ali Osman Saatci, MD).

OCTA detection limits [143]. Lee et al. [144] addressed segmentation challenges by manually adjusting the SCP/DCP boundary in severe DME cases, revealing significant DCP damage, particularly in poor responders to anti-VEGF therapy. This underscores the critical role of DCP integrity as a biomarker for treatment response prediction in DME. Longitudinal studies, such as those by Sun et al. [139], highlight the predictive value of SCP VD in identifying individuals at risk of developing DME over time. As OCTA technology advances and more studies are conducted, its role in the comprehensive management of DME is expected to expand significantly. **Figure 9** shows the OCTA image of a patient with severe DME.

4. Conclusions

In conclusion, OCT and OCTA provide valuable insights into the pathophysiology, diagnosis, and management of DR and DME. OCT biomarkers offer critical information on disease severity, prognosis, and treatment response. Similarly, OCTA metrics enhance our understanding of microvascular changes in DR. These biomarkers facilitate early detection, precise monitoring, and tailored therapeutic strategies, ultimately improving visual outcomes for patients with DR and DME. The integration of OCT and OCTA in clinical practice underscores their indispensable role in advancing diabetic eye care, offering non-invasive, high-resolution imaging that supports comprehensive disease management. Future research should continue to refine these biomarkers, address current limitations, and explore their full potential in enhancing patient care and outcomes.

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References

- [1] Kumar A, Gangwar R, Zargar AA, Kumar R, Sharma A. Prevalence of diabetes in India: A review of IDF diabetes atlas 10th edition. *Current Diabetes Reviews.* 2024;20(1):e130423215752
- [2] Teo ZL et al. Global prevalence of diabetic retinopathy and projection of burden through 2045: Systematic review and meta-analysis. *Ophthalmology.* 2021;128(11):1580-1591
- [3] Wang W, Lo ACY. Diabetic retinopathy: Pathophysiology and treatments. *International Journal of Molecular Sciences.* 2018;19(6):1816. DOI: 10.3390/ijms19061816
- [4] Sabanayagam C, Yip W, Ting DSW, Tan G, Wong TY. Ten emerging trends in the epidemiology of diabetic retinopathy. *Ophthalmic Epidemiology.* 2016;23(4):209-222
- [5] Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. *Progress in Retinal and Eye Research.* 2018;64:1-55
- [6] Virgili G et al. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *Cochrane Database of Systematic Reviews.* 2015;1(1):CD008081
- [7] Zhang Y et al. Prediction of visual acuity after anti-VEGF therapy in diabetic macular edema by machine learning. *Journal Diabetes Research.* 2022;2022:5779210
- [8] Zhou J, Song S, Zhang Y, Jin K, Ye J. OCT-based biomarkers are associated with systemic inflammation in patients with treatment-Naïve diabetic macular edema. *Ophthalmology and Therapy.* 2022;11(6):2153-2167
- [9] Visioli G et al. OCT biomarkers as predictors of visual improvement in diabetic macular edema eyes receiving dexamethasone implants. *International Journal of Retina and Vitreous.* 2023;9(1):35
- [10] Sun Z, Yang D, Tang Z, Ng DS, Cheung CY. Optical coherence tomography angiography in diabetic retinopathy: An updated review. *Eye (London).* 2021;35(1):149-161
- [11] Markan A, Agarwal A, Arora A, Bazgain K, Rana V, Gupta V. Novel imaging biomarkers in diabetic retinopathy and diabetic macular edema. *Therapeutic Advances in Ophthalmology.* 2020;12:2515841420950513
- [12] Saxena S et al. Spectral domain optical coherence tomography based imaging biomarkers for diabetic retinopathy. *Endocrine.* 2019;66(3):509-516
- [13] Bressler NM et al. Persistent macular thickening following intravitreous afibbercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: A secondary analysis of a randomized clinical trial. *JAMA Ophthalmology.* 2018;136(3):257-269
- [14] Pieramici DJ, Wang P-W, Ding B, Gune S. Visual and anatomic outcomes in patients with diabetic macular edema with limited initial anatomic response to ranibizumab in RIDE and RISE. *Ophthalmology.* 2016;123(6):1345-1350
- [15] Wells JA et al. Afibbercept, bevacizumab, or ranibizumab for diabetic macular edema. *The New England Journal of Medicine.* 2015;372(13):1193-1203

- [16] Karst SG et al. Atrophy of the central neuroretina in patients treated for diabetic macular edema. *Acta Ophthalmologica*. 2019;97(8):e1054-e1061
- [17] Hannouche RZ, de Avila MP, Isaac DLC, e Silva RSC, Rassi AR. Correlation between central subfield thickness, visual acuity and structural changes in diabetic macular edema. *Arquivos Brasileiros de Oftalmologia*. 2012;75(3):183-187
- [18] Maheshwary AS, Oster SF, Yuson RMS, Cheng L, Mojana F, Freeman WR. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. *American Journal of Ophthalmology*. 2010;150(1):63-67.e1
- [19] Yalçın NG, Özdek S. The relationship between macular cyst formation and ischemia in diabetic macular edema. *Turkish Journal of Ophthalmology*. 2019;49(4):194-200
- [20] Panozzo G et al. An optical coherence tomography-based grading of diabetic maculopathy proposed by an international expert panel: The European school for advanced studies in ophthalmology classification. *European Journal of Ophthalmology*. 2020;30(1):8-18
- [21] Reznicek L et al. Functional and morphological changes in diabetic macular edema over the course of anti-vascular endothelial growth factor treatment. *Acta Ophthalmologica*. 2013;91(7):e529-e536
- [22] Karst SG et al. Detailed analysis of retinal morphology in patients with diabetic macular edema (DME) randomized to ranibizumab or triamcinolone treatment. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht von Graefes Archiv fur Klinische und Experimentelle Ophthalmologie*. 2018;256(1):49-58
- [23] Huang Y-T et al. Optical coherence tomography biomarkers in predicting treatment outcomes of diabetic macular edema after dexamethasone implants. *Frontiers in Medicine*. 2022;9:852022
- [24] Khoramnia R et al. Exploring the role of retinal fluid as a biomarker for the management of diabetic macular oedema. *Eye (London)*. 2024;38(1):54-60
- [25] Park J, Felfeli T, Kherani IZ, Altomare F, Chow DR, Wong DT. Prevalence and clinical implications of subretinal fluid in retinal diseases: A real-world cohort study. *BMJ Open Ophthalmology*. 2023;8(1):e001214. DOI: 10.1136/bmjophth-2022-001214
- [26] Fickweiler W, Schauvlieghe A-SME, Schlingemann RO, Maria Hooymans JM, Los LI, Verbraak FD. Predictive value of optical coherence tomographic features In the bevacizumab and ranibizumab In patients with diabetic macular edema (BRDME) study. *Retina*. 2018;38(4):812-819
- [27] Korobelnik J-F et al. Effect of baseline subretinal fluid on treatment outcomes in VIVID-DME and VISTA-DME studies. *Ophthalmology Retina*. 2019;3(8):663-669
- [28] Bressler SB et al. Factors associated with visual acuity and central subfield thickness changes when treating diabetic macular edema with anti-vascular endothelial growth factor therapy: An exploratory analysis of the protocol T randomized clinical trial. *JAMA Ophthalmology*. 2019;137(4):382-389
- [29] Szeto SK et al. OCT-based biomarkers for predicting treatment response in eyes

- with centre-involved diabetic macular oedema treated with anti-VEGF injections: A real-life retina clinic-based study. *The British Journal of Ophthalmology.* 2023;107(4):525-533
- [30] Shimura M et al. Visual outcome after intravitreal triamcinolone acetonide depends on optical coherence tomographic patterns in patients with diffuse diabetic macular edema. *Retina.* 2011;31(4):748-754
- [31] Grunwald JE et al. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology.* 2014;121(1):150-161
- [32] Joltikov KA et al. Disorganization of retinal inner layers (DRIL) and neuroretinal dysfunction in early diabetic retinopathy. *Investigative Ophthalmology & Visual Science.* 2018;59(13):5481-5486
- [33] Khojasteh H et al. Multifocal electroretinogram in diabetic macular edema and its correlation with different optical coherence tomography features. *International Ophthalmology.* 2020;40(3):571-581
- [34] Pelosini L, Hull CC, Boyce JF, McHugh D, Stanford MR, Marshall J. Optical coherence tomography may be used to predict visual acuity in patients with macular edema. *Investigative Ophthalmology & Visual Science.* 2011;52(5):2741-2748
- [35] Tsai W-S et al. Characterization of the structural and functional alteration in eyes with diabetic macular ischemia. *Ophthalmology Retina.* 2023;7(2):142-152
- [36] Nadri G et al. Disorganization of retinal inner layers correlates with ellipsoid zone disruption and retinal nerve fiber layer thinning in diabetic retinopathy. *Journal of Diabetes and its Complications.* 2019;33(8):550-553
- [37] Das R, Spence G, Hogg RE, Stevenson M, Chakravarthy U. Disorganization of inner retina and outer retinal morphology in diabetic macular edema. *JAMA Ophthalmology.* 2018;136(2):202-208
- [38] Balaratnasingam C et al. Visual acuity is correlated with the area of the foveal avascular zone in diabetic retinopathy and retinal vein occlusion. *Ophthalmology.* 2016;123(11):2352-2367
- [39] Zur D et al. Disorganization of retinal inner layers as a biomarker in patients with diabetic macular oedema treated with dexamethasone implant. *Acta Ophthalmologica.* 2020;98(2):e217-e223
- [40] Sun JK et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. *JAMA Ophthalmology.* 2014;132(11):1309-1316
- [41] Vujosevic S et al. Diabetic macular edema with neuroretinal detachment: OCT and OCT-angiography biomarkers of treatment response to anti-VEGF and steroids. *Acta Diabetologica.* 2020;57(3):287-296
- [42] Munk MR, Somfai GM, de Smet MD, et al. The role of intravitreal corticosteroids in the treatment of DME: predictive OCT biomarkers. *International Journal of Molecular Sciences.* 2022;23(14):7585. Published 2022 Jul 8. DOI: 10.3390/ijms23147585
- [43] Vujosevic S, Bini S, Midena G, Berton M, Pilotto E, Midena E. Hyperreflective intraretinal spots in diabetics without and with nonproliferative diabetic retinopathy: An in vivo study using spectral domain OCT.

Journal Diabetes Research.
2013;2013:491835

[44] Szeto SK et al. Optical coherence tomography in the management of diabetic macular oedema. *Progress in Retinal and Eye Research.*
2024;98:101220

[45] Bolz M, Schmidt-Erfurth U, Deak G, Mylonas G, Kriechbaum K, Scholda C. Optical coherence tomographic hyperreflective foci: A morphologic sign of lipid extravasation in diabetic macular edema. *Ophthalmology.* 2009;116(5):914-920

[46] Vujosevic S, Torresin T, Berton M, Bini S, Convento E, Midena E. Diabetic macular edema with and without subfoveal neuroretinal detachment: Two different morphologic and functional entities. *American Journal of Ophthalmology.* 2017;181:149-155

[47] Vujosevic S et al. Imaging retinal inflammatory biomarkers after intravitreal steroid and anti-VEGF treatment in diabetic macular oedema. *Acta Ophthalmologica.*
2017;95(5):464-471

[48] Chatziralli IP, Sergentanis TN, Sivaprasad S. Hyperreflective foci as an independent visual outcome predictor In macular edema due to retinal vascular diseases treated with intravitreal dexamethasone or ranibizumab. *Retina.*
2016;36(12):2319-2328

[49] Huang C-H, Yang C-H, Hsieh Y-T, Yang C-M, Ho T-C, Lai T-T. Hyperreflective foci in predicting the treatment outcomes of diabetic macular oedema after anti-vascular endothelial growth factor therapy. *Scientific Reports.*
2021;11(1):5103

[50] Kang J-W, Chung H, Chan Kim H. Correlation of optical coherence

tomographic hyperreflective foci with visual outcomes in different patterns of diabetic macular edema. *Retina.*
2016;36(9):1630-1639

[51] Gelman SK, Freund KB, Shah VP, Sarraf D. The pearl necklace sign: A novel spectral domain optical coherence tomography finding in exudative macular disease. *Retina.* 2014;34(10):2088-2095

[52] Ajay K, Mason F, Gonglore B, Bhatnagar A. Pearl necklace sign in diabetic macular edema: Evaluation and significance. *Indian Journal of Ophthalmology.* 2016;64(11):829-834

[53] Omri S et al. The outer limiting membrane (OLM) revisited: Clinical implications. *Clinical Ophthalmology.*
2010;4:183-195

[54] Becker S, Carroll LS, Vinberg F. Diabetic photoreceptors: Mechanisms underlying changes in structure and function. *Visual Neuroscience.*
2020;37:E008

[55] Saxena S, Srivastav K, Cheung CM, Ng JY, Lai TY. Photoreceptor inner segment ellipsoid band integrity on spectral domain optical coherence tomography. *Clinical Ophthalmology.*
2014;8:2507-2522

[56] Wu Z, Ayton LN, Guymer RH, Luu CD. Second reflective band intensity in age-related macular degeneration. *Ophthalmology.* 2013;120(6):1307-8.e1

[57] Borrelli E, Palmieri M, Viggiano P, Ferro G, Mastropasqua R. Photoreceptor damage in diabetic choroidopathy. *Retina.* 2020;40(6):1062-1069

[58] Forooghian F et al. Relationship between photoreceptor outer segment length and visual acuity in diabetic macular edema. *Retina.*
2010;30(1):63-70

- [59] Achiron A et al. Photoreceptor integrity predicts response to anti-VEGF treatment. *Ophthalmic Research*. 2017;57(1):37-41
- [60] Serizawa S, Ohkoshi K, Minowa Y, Soejima K. Interdigitation zone band restoration after treatment of diabetic macular edema. *Current Eye Research*. 2016;41(9):1229-1234
- [61] Koc F, Güven YZ, Egrilmez D, Aydin E. Optical coherence tomography biomarkers in bilateral diabetic macular edema patients with asymmetric anti-VEGF response. *Seminars in Ophthalmology*. 2021;36(5-6):444-451
- [62] Zur D, Iglicki M, Busch C, Invernizzi A, Mariussi M, Loewenstein A. OCT biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. *Ophthalmology*. 2018;125(2):267-275
- [63] Ehlers JP et al. Higher-order assessment of OCT in diabetic macular edema from the VISTA study: Ellipsoid zone dynamics and the retinal fluid index. *Ophthalmology Retina*. 2019;3(12):1056-1066
- [64] Damian I, Nicoara SD. Optical coherence tomography biomarkers of the outer blood-retina barrier in patients with diabetic macular oedema. *Journal Diabetes Research*. 2020;2020:8880586
- [65] Boynton GE, Stem MS, Kwark L, Jackson GR, Farsiu S, Gardner TW. Multimodal characterization of proliferative diabetic retinopathy reveals alterations in outer retinal function and structure. *Ophthalmology*. 2015;122(5):957-967
- [66] Tavares Ferreira J et al. Retinal neurodegeneration in diabetic patients without diabetic retinopathy.
- Investigative Ophthalmology & Visual Science. 2016;57(14):6455-6460
- [67] Arrigo A et al. Foveal eversion patterns in diabetic macular edema. *Scientific Reports*. 2022;12(1):13097
- [68] Uji A et al. Parallelism for quantitative image analysis of photoreceptor-retinal pigment epithelium complex alterations in diabetic macular edema. *Investigative Ophthalmology & Visual Science*. 2014;55(5):3361-3367
- [69] Noma H, Yasuda K, Shimura M. Involvement of cytokines in the pathogenesis of diabetic macular edema. *International Journal of Molecular Sciences*. Mar 2021;22(7):3427. DOI: 10.3390/ijms22073427
- [70] Nasrallah FP et al. The role of the vitreous in diabetic macular edema. *Ophthalmology*. 1988;95(10):1335-1339
- [71] Hikichi T, Fujio N, Akiba J, Azuma Y, Takahashi M, Yoshida A. Association between the short-term natural history of diabetic macular edema and the vitreomacular relationship in type II diabetes mellitus. *Ophthalmology*. 1997;104(3):473-478
- [72] Schmidt-Erfurth U et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica Journal International d'ophtalmologie*. *International Journal Ophthalmology Zeitschrift fur Augenheilkde*. 2017;237(4):185-222
- [73] Sadiq MA et al. Effect of vitreomacular adhesion on treatment outcomes in the ranibizumab for edema of the macula in diabetes (READ-3) study. *Ophthalmology*. 2016;123(2):324-329

- [74] Yanoff M. Ocular pathology of diabetes mellitus. *American Journal of Ophthalmology.* 1969;67(1):21-38
- [75] Hidayat AA, Fine BS. Diabetic choroidopathy. Light and electron microscopic observations of seven cases. *Ophthalmology.* 1985;92(4):512-522
- [76] Kim JT, Lee DH, Joe SG, Kim J-G, Yoon YH. Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. *Investigative Ophthalmology & Visual Science.* 2013;54(5):3378-3384
- [77] Eliwa TF, Hegazy OS, Mahmoud SS, Almaamon T. Choroidal thickness change in patients with diabetic macular edema. *Ophthalmic Surgery, Lasers & Imaging Retina.* 2017;48(12):970-977
- [78] Querques G et al. Enhanced depth imaging optical coherence tomography in type 2 diabetes. *Investigative Ophthalmology & Visual Science.* 2012;53(10):6017-6024
- [79] Choi W et al. Ultrahigh speed swept source optical coherence tomography angiography of retinal and choriocapillaris alterations In diabetic patients with and without retinopathy. *Retina.* 2017;37(1):11-21
- [80] Nisper PL et al. Quantifying microvascular abnormalities with increasing severity of diabetic retinopathy using optical coherence tomography angiography. *Investigative Ophthalmology & Visual Science.* 2017;58(6):BIO307-BIO315
- [81] Wang W et al. Choroidal thickness in diabetes and diabetic retinopathy: A swept source OCT study. *Investigative Ophthalmology & Visual Science.* 2020;61(4):29
- [82] Sakanishi Y, Morita S, Mashimo K, Tamaki K, Ebihara N. Subfoveal choroidal thickness and treatment outcomes of intravitreal aflibercept for branch retinal vein occlusion. *Life (Basel).* Jun 2021;11(6):572. DOI: 10.3390/life11060572
- [83] Xu J et al. Subfoveal choroidal thickness in diabetes and diabetic retinopathy. *Ophthalmology.* 2013;120(10):2023-2028
- [84] Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. *Investigative Ophthalmology & Visual Science.* 2012;53(1):261-266
- [85] Moon KY, Choi SY, Song JH. Changes in subfoveal choroidal thickness after intravitreal dexamethasone implant therapy for diabetic macular edema. *Retina.* 2021;41(6):1283-1292
- [86] Campos A et al. Choroidal thickness changes stratified by outcome in real-world treatment of diabetic macular edema. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht von Graefes Archiv fur Klinische und Experimentelle Ophthalmologie.* 2018;256(10):1857-1865
- [87] Wang X-N, Cai X, He S, Zhang X, Wu Q. Subfoveal choroidal thickness changes after intravitreal ranibizumab injections in different patterns of diabetic macular edema using a deep learning-based auto-segmentation. *International Ophthalmology.* 2023;43(12):4399-4407
- [88] Yiu G, Manjunath V, Chiu SJ, Farsiu S, Mahmoud TH. Effect of anti-vascular endothelial growth factor therapy on choroidal thickness in diabetic macular edema. *American*

Journal of Ophthalmology.
2014;158(4):745-751.e2

[89] Sonoda S et al. Choroidal structure in normal eyes and after photodynamic therapy determined by binarization of optical coherence tomographic images. *Investigative Ophthalmology & Visual Science*. 2014;55(6):3893-3899

[90] Unsal E, Eltutar K, Zirtiloğlu S, Dinçer N, Ozdoğan Erkul S, Güngel H. Choroidal thickness in patients with diabetic retinopathy. *Clinical Ophthalmology*. 2014;8:637-642

[91] Keskin Ç, Dilekçi ENA, Üçgül AY, Üçgül RK, Toprak G, Cengiz D. Choroidal vascularity index as a predictor for the development of retinopathy in diabetic patients. *Journal of Endocrinological Investigation*. 2024;47(5):1175-1180

[92] Kim M, Ha MJ, Choi SY, Park Y-H. Choroidal vascularity index in type-2 diabetes analyzed by swept-source optical coherence tomography. *Scientific Reports*. 2018;8(1):70

[93] Dou N et al. Choroidal vascularity index as a biomarker for visual response to antivascular endothelial growth factor treatment in diabetic macular edema. *Journal Diabetes Research*. 2021;2021:3033219

[94] Roy R, Saurabh K, Shah D, Chowdhury M, Goel S. Choroidal hyperreflective foci: A novel spectral domain optical coherence tomography biomarker in eyes with diabetic macular edema. *Asia-Pacific Journal of Ophthalmology* (Philadelphia, Pa.). 2019;8(4):314-318

[95] Saurabh K, Roy R, Herekar S, Mistry S, Choudhari S. Validation of choroidal hyperreflective foci in diabetic macular edema through a

retrospective pilot study. *Indian Journal of Ophthalmology*. 2021;69(11):3203-3206

[96] Hirano T, Kitahara J, Toriyama Y, Kasamatsu H, Murata T, Sadda S. Quantifying vascular density and morphology using different swept-source optical coherence tomography angiographic scan patterns in diabetic retinopathy. *The British Journal of Ophthalmology*. 2019;103(2):216-221

[97] Ho J, Dans K, You Q, Nudleman ED, Freeman WR. Comparison of 3 mm × 3 mm versus 6 mm × 6 mm optical coherence tomography angiography scan sizes In the evaluation of non-proliferative diabetic retinopathy. *Retina*. 2019;39(2):259-264

[98] Samara WA et al. Correlation of foveal avascular zone size with foveal morphology in normal eyes using optical coherence tomography angiography. *Retina*. 2015;35(11):2188-2195

[99] Tang FY et al. Clinically relevant factors associated with quantitative optical coherence tomography angiography metrics in deep capillary plexus in patients with diabetes. *Eye and Vision* (London, England). 2020;7:7

[100] Cennamo G, Montorio D, Fossataro F, Fossataro C, Tranfa F. Evaluation of vessel density in disorganization of retinal inner layers after resolved diabetic macular edema using optical coherence tomography angiography. *PLoS One*. 2021;16(1):e0244789

[101] de Carlo TE et al. Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. *Retina*. 2015;35(11):2364-2370

- [102] Takase N, Nozaki M, Kato A, Ozeki H, Yoshida M, Ogura Y. Enlargement of foveal avascular zone in diabetic eyes evaluated by en face optical coherence tomography angiography. *Retina.* 2015;35(11):2377-2383
- [103] Dai Y et al. Microvascular changes in the choriocapillaris of diabetic patients without retinopathy investigated by swept-source OCT angiography. *Investigative Ophthalmology & Visual Science.* 2020;61(3):50
- [104] Wang F, Saraf SS, Zhang Q, Wang RK, Rezaei KA. Ultra-widefield protocol enhances automated classification of diabetic retinopathy severity with OCT angiography. *Ophthalmology Retina.* 2020;4(4):415-424
- [105] Lee J, Rosen R. Optical coherence tomography angiography in diabetes. *Current Diabetes Reports.* 2016;16(12):123
- [106] Reste-Ferreira D et al. Retinal neurodegeneration in eyes with NPDR risk phenotypes: A two-year longitudinal study. *Acta Ophthalmologica.* 2024;102(4):e539-e547
- [107] Durbin MK et al. Quantification of retinal microvascular density in optical coherence tomographic angiography images in diabetic retinopathy. *JAMA Ophthalmology.* 2017;135(4):370-376
- [108] Bin Lim H, Kim YW, Kim JM, Jo YJ, Kim JY. The importance of signal strength in quantitative assessment of retinal vessel density using optical coherence tomography angiography. *Scientific Reports.* 2018;8(1):12897
- [109] Santos T et al. Swept-source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR. *The British Journal of Ophthalmology.* 2022;106(5):712-718
- [110] Veiby NCBB et al. Associations between macular OCT angiography and nonproliferative diabetic retinopathy in young patients with type 1 diabetes mellitus. *Journal Diabetes Research.* 2020;2020:8849116
- [111] Bek T. Transretinal histopathological changes in capillary-free areas of diabetic retinopathy. *Acta Ophthalmologica.* 1994;72(4):409-415
- [112] Onishi AC et al. Importance of considering the middle capillary plexus on OCT angiography in diabetic retinopathy. *Investigative Ophthalmology & Visual Science.* 2018;59(5):2167-2176
- [113] Chouhan S, Kalluri Bharat RP, Surya J, et al. Preliminary report on optical coherence tomography angiography biomarkers in non-responders and responders to intravitreal anti-VEGF injection for diabetic macular oedema. *Diagnostics (Basel).* 2023;13(10):1735. Published 2023 May 13. DOI: 10.3390/diagnostics13101735
- [114] Zheng F et al. Age-dependent changes in the macular choriocapillaris of normal eyes imaged with swept-source optical coherence tomography angiography. *American Journal of Ophthalmology.* 2019;200:110-122
- [115] McLeod DS, Lutty GA. High-resolution histologic analysis of the human choroidal vasculature. *Investigative Ophthalmology & Visual Science.* 1994;35(11):3799-3811
- [116] Chu Z et al. Quantitative assessment of the retinal microvasculature using optical coherence tomography angiography. *Journal of Biomedical Optics.* 2016;21(6):66008
- [117] Sasongko MB, Wong TY, Nguyen TT, Cheung CY, Shaw JE,

Wang JJ. Retinal vascular tortuosity in persons with diabetes and diabetic retinopathy. *Diabetologia*. 2011;54(9):2409-2416

[118] Klein R, Meuer SM, Moss SE, Klein BE. Retinal microaneurysm counts and 10-year progression of diabetic retinopathy. *Archives of Ophthalmology* (Chicago, Ill. 1960). 1995;113(11):1386-1391

[119] Thompson IA, Durrani AK, Patel S. Optical coherence tomography angiography characteristics in diabetic patients without clinical diabetic retinopathy. *Eye* (London). 2019;33(4):648-652

[120] Couturier A et al. Capillary plexus anomalies in diabetic retinopathy on optical coherence tomography angiography. *Retina*. 2015;35(11):2384-2391

[121] Parravano M et al. Diabetic microaneurysms internal reflectivity on spectral-domain optical coherence tomography and optical coherence tomography angiography detection. *American Journal of Ophthalmology*. 2017;179:90-96

[122] Park JJ, Soetikno BT, Fawzi AA. Characterization of the middle capillary plexus using optical coherence tomography angiography in healthy and diabetic eyes. *Retina*. 2016;36(11):2039-2050

[123] Pan J et al. Characteristics of neovascularization in early stages of proliferative diabetic retinopathy by optical coherence tomography angiography. *American Journal of Ophthalmology*. 2018;192:146-156

[124] Arya M et al. Distinguishing intraretinal microvascular abnormalities from retinal neovascularization using

optical coherence tomography angiography. *Retina*. 2020;40(9):1686-1695

[125] Hwang TS et al. Optical coherence tomography angiography features of diabetic retinopathy. *Retina*. 2015;35(11):2371-2376

[126] Motulsky EH et al. Widefield swept-source optical coherence tomography angiography of proliferative diabetic retinopathy. *Ophthalmic Surgery, Lasers & Imaging Retina*. 2019;50(8):474-484

[127] Russell JF et al. Longitudinal wide-field swept-source OCT angiography of neovascularization in proliferative diabetic retinopathy after panretinal photocoagulation. *Ophthalmology Retina*. 2019;3(4):350-361

[128] Faghihi H et al. Effect of panretinal photocoagulation on macular vasculature using optical coherence tomography angiography. *European Journal of Ophthalmology*. 2021;31(4):1877-1884

[129] Acar OPA, Onur IU. Effect of panretinal photocoagulation on retina and choroid in diabetic retinopathy: An optical coherence tomography angiography study. *Photodiagnosis and Photodynamic Therapy*. 2022;40:103166

[130] Bhardwaj S et al. Value of fractal analysis of optical coherence tomography angiography in various stages of diabetic retinopathy. *Retina*. 2018;38(9):1816-1823

[131] Kim AY, Chu Z, Shahidzadeh A, Wang RK, Puliafito CA, Kashani AH. Quantifying microvascular density and morphology in diabetic retinopathy using spectral-domain optical coherence tomography angiography. *Investigative*

Ophthalmology & Visual Science.
2016;57(9):OCT362-OCT370

[132] Serra R et al. Optical coherence tomography angiography macular biomarkers of peripheral retinal ischemia in diabetic macular edema: Secondary endpoints from the clinical study 'FOVEA'. Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht von Graefes Archiv fur Klinische und Experimentelle Ophthalmologie. 2024;262(6):1777-1783

[133] Barot M, Gokulgandhi MR, Patel S, Mitra AK. Microvascular complications and diabetic retinopathy: Recent advances and future implications. Future Medicinal Chemistry. 2013;5(3):301-314

[134] Fan W et al. Relationship between retinal fractal dimension and nonperfusion in diabetic retinopathy on ultrawide-field fluorescein angiography. American Journal of Ophthalmology. 2020;209:99-106

[135] Bhanushali D et al. Linking retinal microvasculature features with severity of diabetic retinopathy using optical coherence tomography angiography. Investigative Ophthalmology & Visual Science. 2016;57(9):OCT519-OCT525

[136] Mendes L, Marques IP, Cunha-Vaz J. Comparison of different metrics for the identification of vascular changes in diabetic retinopathy using OCTA. Frontiers in Neuroscience. 2021;15:755730

[137] Kashani AH et al. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Progress in Retinal and Eye Research. 2017;60:66-100

[138] Kashani AH et al. Suspended scattering particles in motion: A novel

feature of OCT angiography in exudative maculopathies. Ophthalmology Retina. 2018;2(7):694-702

[139] Sun Z et al. OCT angiography metrics predict progression of diabetic retinopathy and development of diabetic macular edema: A prospective study. Ophthalmology. 2019;126(12):1675-1684

[140] Hasegawa N, Nozaki M, Takase N, Yoshida M, Ogura Y. New insights into microaneurysms in the deep capillary plexus detected by optical coherence tomography angiography in diabetic macular edema. Investigative Ophthalmology & Visual Science. 2016;57(9):OCT348-OCT355

[141] Nanegrungsunk O, Patikulsila D, Sadda SR. Ophthalmic imaging in diabetic retinopathy: A review. Clinical & Experimental Ophthalmology. 2022;50(9):1082-1096

[142] Suciu C-I, Suciu V-I, Nicoara S-D. Optical coherence tomography (angiography) biomarkers in the assessment and monitoring of diabetic macular edema. Journal Diabetes Research. 2020;2020:6655021

[143] de Carlo TE et al. Distinguishing diabetic macular edema from capillary nonperfusion using optical coherence tomography angiography. Ophthalmic Surgery, Lasers & Imaging Retina. 2016;47(2):108-114

[144] Lee J, Moon BG, Cho AR, Yoon YH. Optical coherence tomography angiography of DME and its association with anti-VEGF treatment response. Ophthalmology. 2016;123(11):2368-2375