Chapter

Optical Coherence Tomography in Diabetic Retinopathy

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Abstract

Optical coherence tomography (OCT) has become an indispensable modality of investigation in the assessment of diabetic retinopathy. It is a non-invasive and reliable imaging tool that provides a comprehensive analysis of the retina. The images are obtained very fast. It is useful for quantitative as well as qualitative assessment of structural changes that occur in diabetic retinopathy. It also enables the detection of subclinical diabetic macular edema. Various imaging biomarkers have been identified on OCT imaging. These markers help prognosticate the case and determine treatment response. The follow-up imaging helps assess the response to treatment and detect recurrence of disease or need for further treatment.

Keywords: spectral-domain optical coherence tomography, swept-source optical coherence tomography, diabetic macular edema, optical coherence tomography angiography, imaging biomarkers

1. Introduction

Diabetes Mellitus (DM) is a disease characterized by elevated blood glucose levels due to its impaired metabolism. It is principally classified into Type 1 DM and Type 2 DM, the former being defined by the absence of insulin secretion whereas resistance to insulin defines the latter. According to the figures analyzed at the global level, diabetes is expected to affect 629 million people by 2045 in the age category of 20 to 79 years [1]. Long-term uncontrolled DM leads to both macrovascular and microvascular complications. Diabetic Retinopathy (DR), a microvascular complication, affects one-third of the population suffering from diabetes [2, 3]. The pathology of DR involves capillary endothelial cell proliferation, thickening of the basement membrane, and loss of pericytes, leading to the formation of microaneurysms, increase in vessel permeability, and the destruction of the blood-retinal barrier. This leads to the accumulation of fluid within and beneath the layers of the retina, causing diabetic macular edema (DME). Diabetic retinopathy is the leading cause of blindness in individuals of the working-age group [4]. In more advanced cases, capillary blockage and ischemia result in the formation of new blood vessels, resulting in proliferative diabetic retinopathy (PDR).

The definition of clinically significant macular edema in diabetes was given by the Early Treatment Diabetic Retinopathy Study (ETDRS) where slit-lamp biomicroscopy or stereoscopic fundus photography was used to identify retinal thickening and hard exudates [5]. However, the use of slit-lamp biomicroscopy or color fundus photography for examining macular edema is subjective and may fail to detect mild changes in retinal thickness. Biomicroscopy does not provide information regarding the exact retinal layer involved. Fundus fluorescein angiography

(FA) is an investigation modality that is used to classify DME into focal and diffuse based on the leakage pattern. This classification helps in guiding focal laser treatment to leaking microaneurysms or grid laser to the leaking capillaries. Ischemic areas and macular ischemia are also well identified on FA. Though FA offers useful information, it is also a subjective test and retinal thickness or morphology cannot be assessed on FA. The advent of optical coherence tomography (OCT), has improved the understanding of DME.

OCT has rapidly grown to become a routine tool of investigation in ophthalmology. Its various advantages lie in the fact that it provides an objective, non-invasive, high resolution, reproducible, and cross-sectional image of the retina [6]. It does not require a highly skilled person for its operation, or pharmacological dilation of the pupil. It is sensitive to identify even mild changes in retinal morphology that are often not visible to the naked eye on clinical examination.

2. Principle and technique

In simple terms, OCT is similar to ultrasound in that a beam of sound or light directed onto a tissue is differentially reflected from structures with different acoustic or optical properties. The time it takes for the sound or light to reflect from the

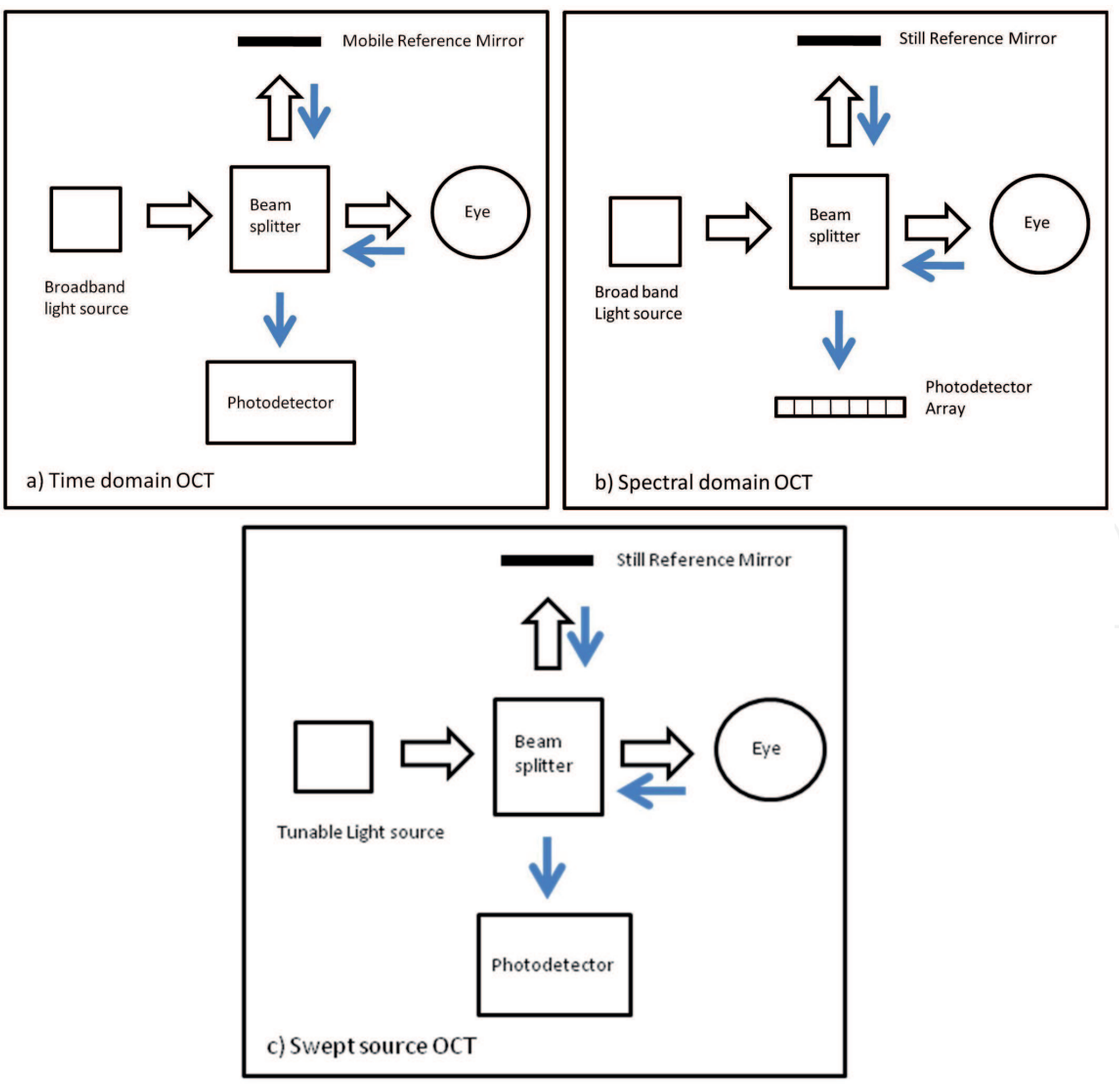

Figure 1.
a) Principle of time domain OCT. b) Principle of spectral domain OCT. c) Principle of swept source OCT.

different structures determines the dimensions of the structures. This provides an image similar to the A-scan or depth scan of ultrasound. Imaging of laterally adjacent depth scans provides a two-dimensional or B-scan image. The time delay involved when using light is in femtoseconds requiring interferometry to do the calculations [7].

The first generation OCT machine or Time-Domain OCT (TD-OCT) uses low time-coherence interferometry to obtain depth scans (**Figure 1a**). A beam splitter splits the light coming from a broadband light source, one directed to the eye and the other to the reference mirror. The position of the reference mirror is changed to mirror the depth of the various layers of tissue being scanned. Light reflected from the two sources is collected and the interferogram is analyzed to give a complete depth scan. TD-OCT involves two scans, one for depth scan and one for lateral scan, thus, resulting in a lesser number of scans acquired per second.

With the use of spectrometer and Fourier-domain technique in the next generation OCT, called Spectral-domain OCT (SD-OCT), the disadvantage of performing a depth scan was avoided. SD-OCT uses an array of photo-detectors to capture the depth scan without having to move the reference mirror (**Figure 1b**). Therefore, only a lateral scan has to be performed [7]. This increased the scan speed enormously. Further refinement of technology led to the change of the broadband near-infrared superluminescent diode light source of wavelength 840 nm in SD-OCT to a tunable swept laser source with a center wavelength of 1050 nm [8]. In conjunction, the array of photodetectors in SD-OCT was replaced with a single photodetector [8]. This led to the evolution of Swept-source OCT (SS-OCT) (**Figure 1c**). SS-OCT provides increased scan speed and denser scans with greater resolution as more A-scan and B scans are acquired per second. The scan area is also increased along with scan depth due to the use of a longer wavelength light source which allows better penetration through retinal pigment epithelium (RPE).

3. Normal retinal morphology on optical coherence tomography

The rapid technological evolution of SD-OCT led to the visualization of different hyperreflective and hyporeflective layers of retina commencing from the innermost vitreoretinal interface to the outermost choroid-scleral interface (**Figure 2**) [9]. The innermost layer visualized is the posterior cortical vitreous which is hyperreflective followed by a hyporeflective preretinal space [10]. The innermost layer of the retina is the hyperreflective internal limiting membrane which overlies the retinal nerve fiber layer (RNFL). The next layer is the ganglion cell layer which is less reflective than the RNFL [11]. Outer to the ganglion cell layer is the hyperreflective inner plexiform layer followed by hyporeflective inner nuclear layer. The outer plexiform layer is hyperreflective. OCT has greatly improved the understanding of human anatomy with the identification of Henle's layer as a component of outer half of the outer plexiform layer [12]. Outer to the outer plexiform layer lies the hyporeflective outer nuclear layer. This is followed by the external limiting membrane (ELM), another hyperreflective layer. Latest OCT machines have also made possible, the identification of outer retinal layers that are anatomic correlates of the myoid and ellipsoid (EZ) zones of the inner segment of the photoreceptors [13]. The myoid zone is hyporeflective and lies next to the ELM followed by EZ layer which is hyperreflective. This is followed by the hyporeflective layer of outer segments of photoreceptor and then a hyperreflective interdigitation zone is noted between cone outer segments and apical processes of RPE [13]. The next layer or the outermost layer of the retina is the hyperreflective RPE-Bruch's membrane complex which can be sometimes visualized as separate layers. OCT also helps visualize the components of the choroid [14]. The innermost layer in the choroid is formed by the choriocapillaris. The Sattler's layer

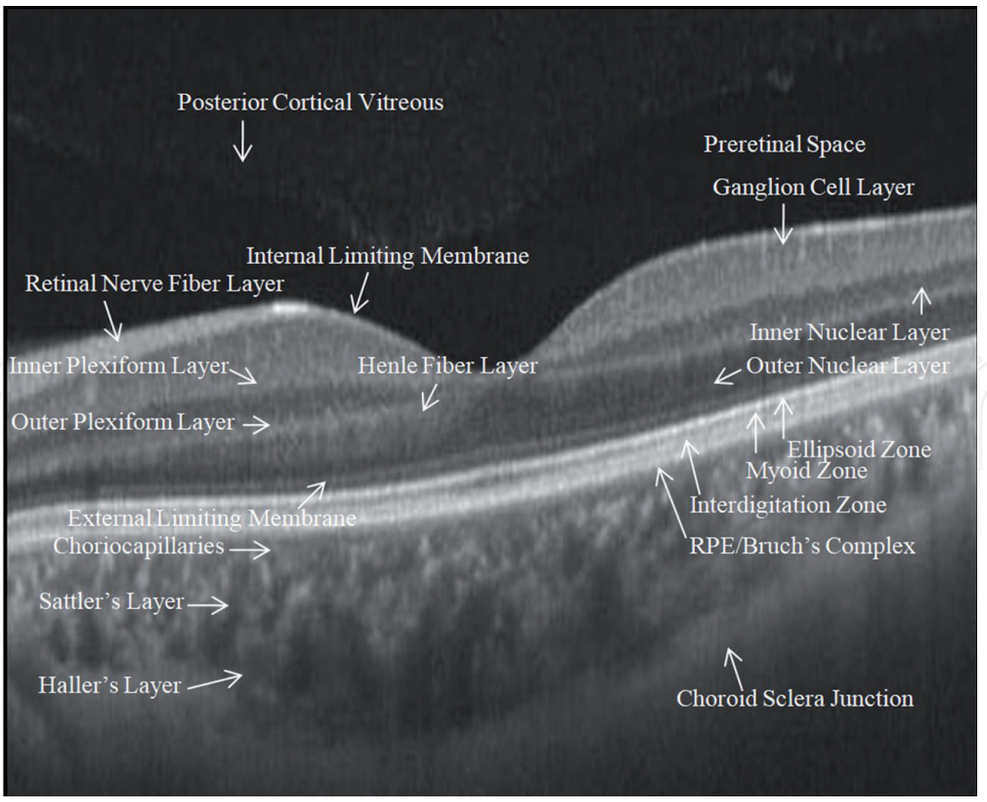

Figure 2.
Normal anatomical landmarks as seen on swept source OCT image.

forms the mid choroid and the Haller's layer forms the outer choroid. The outer boundary of the choroid is the choroidal-scleral junction [14].

Clinically visualized changes of diabetic retinopathy are well delineated on OCT. Hard exudates, cotton wool spots, and epiretinal membrane show hyperreflectivity, edema exhibits hyporeflectivity, and hemorrhages demonstrate backshadowing. Other than these, various discerning features and biomarkers have been identified on OCT which has been discussed later in this chapter.

4. Optical coherence tomography based classification of macular edema

OCT is a sensitive tool to diagnose, quantify, and classify diabetic macular edema. The first OCT-based classification for DME was given by Otani et al [15]. They were the first to identify 3 patterns of fluid accumulation, including sponge-like retinal swelling, cystoid macular edema, and serous retinal detachment (**Figure 3**). They further described that early changes of macular edema were confined to the outer retinal layer mainly the outer plexiform layer when compared to histopathology [15]. With the further accumulation of fluid, the inner retinal layers were involved. The presence of serous retinal detachment in patients with DME is a finding which may not be easily distinguished on biomicroscopy or FA.

In 2004, Panozzo proposed a classification system based on five parameters: retinal thickness, volume, morphology, diffusion, and presence or absence of vitreoretinal traction [16]. They quantified the retinal thickness and volume in three different zones around the fovea. The types of macular edema observed were in agreement with that described by Otani et al., [15] with the only difference being that the size of the cyst was measured to subclassify the grade of the cystoid variety of macular edema. The presence of epiretinal traction and its pattern (tangential or

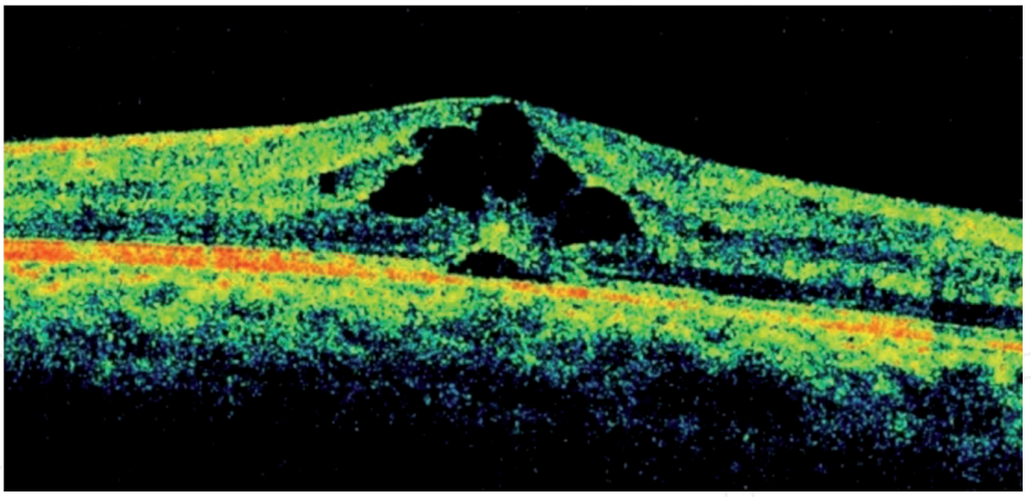

Figure 3.
Cystoid macular edema with presence of serous retinal detachment (spectral-domain OCT).

anteroposterior) were also described. This distinguished cases with an additional component of retinal distortion (**Figure 4**). In 2006, Kim et al. demonstrated similar findings of macular edema and posterior hyaloid traction. In addition, they described tractional retinal detachment as a peak-shaped detachment of the retina [17]. These 3 previous classifications used TD-OCT (**Table 1**).

With the advent of SD-OCT, Murakami et al. for the first time showed that in addition to the morphology of edema, the photoreceptor status played a significant role in the prognosis of visual acuity [18]. They classified edema into serous retinal detachment, cystoid macular edema, and Diffuse type (absence of either cystoid macular edema or serous retinal detachment) with the latter term being used for cases that had retinal thickening but an absence of cysts or serous fluid [18]. Later in 2012, Koleva-Georgieva proposed a classification in which the term early subclinical macular edema was introduced, to describe cases with macular edema which were previously being missed on clinical examination [19]. In addition, they also included the integrity of both the outer retinal layers, the IS/OS (inner segment-outer segment junction, now identified as the EZ layer), and the ELM. Retinal morphology, topography, and presence of traction at macula were also a part of the classification and were similar to the other classifications [19]. In 2013, Helmy et al. further subclassified cystoid macular edema based on the proportion of the largest cyst to the maximum retinal thickness(CME Grade I-IV). The integrity of IS/OS

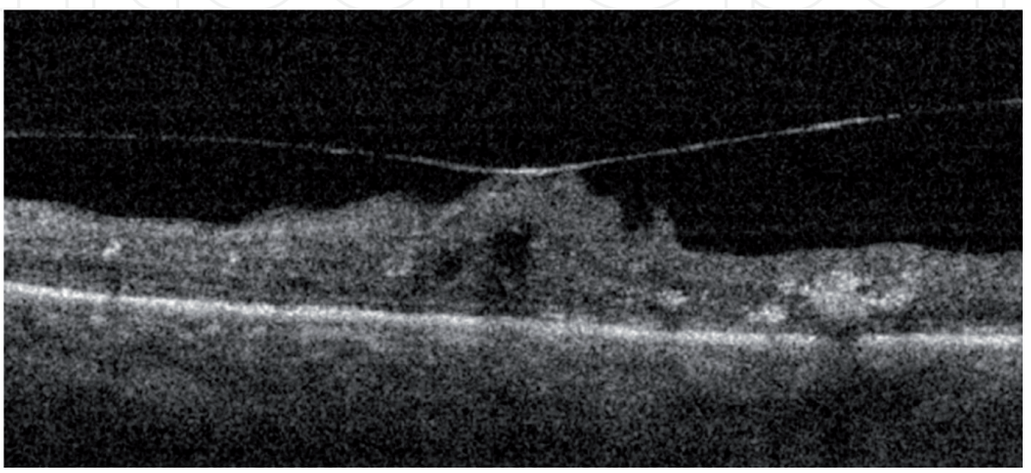

Figure 4.
Vitreomacular traction in a case of diabetic macular edema (captured with SD-OCT).

Classifications based on Time Domain OCT
Otani et al. [15] 1. Sponge-like retinal swelling 2. Cystoid macular edema 3. Serous retinal detachment
Panozzo et al. [16] 1. Retinal thickness 2. Retinal volume 3. Retinal morphology 4. Diffusion 5. Presence of vitreous traction
Kim et al. [17] 1. Diffuse retinal thickening 2. Cystoid macular edema 3. Posterior hyaloidal traction 4. Serous retinal detachment 5. Traction retinal detachment
Classifications based on Spectral Domain OCT
Murakami et al. [18] 1. Serous retinal detachment type 2. Cystoid macular edema type 3. Diffuse type (absence of either cystoid macular edema or serous retinal detachment)
Koleva-Georgieva [19] 1. Retinal thickness 2. Retinal morphology 3. Retinal topography 4. Presence and severity of macular traction 5. Retinal outer layers' integrity (IS/OS and ELM)
Helmy et al. [20] 1. Cystoid macular edema based on the vertical size of the largest macular cyst in proportion to the total macular thickness (CME Grade I-IV) 2. Integrity of External limiting membrane layer and Ellipsoid zone layer (Sub-classification as A-D) [Presence of hyperreflective foci (associated finding)] [Associated neurosensory detachment or vitreomacular traction (associated finding)]
Aiello et al. [21] 1. Center-involved diabetic macular edema 2. Non-center-involved diabetic macular edema

Table 1.
Time domain-OCT and Spectral domain-OCT based classification of Diabetic macular edema.

junction and ELM, presence or absence of neurosensory detachment, or vitreoretinal traction were also included. They extended their classification to include the presence of hyperreflective foci in the outer retina from the ELM to the RPE [20].

5. Role of OCT in treatment of diabetic macular edema

The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents significantly changed the treatment of DME a few years ago [22, 23]. Though laser treatment prescribed by the ETDRS study reduced the risk of vision loss significantly, only 20% of laser-treated eyes experienced a gain in visual acuity of at least 3 lines (15 letters) at 2 years [24]. A study by DRCR.net compared the efficacy of anti-VEGF treatment with laser treatment in eyes with DME [25, 26]. Results showed that anti-VEGF therapy was more effective in preventing the loss of visual acuity. In addition, a significant percentage of eyes showed an improvement in mean visual acuity [25, 26].

Monthly injections and follow-up with OCT imaging of the macula have been recommended in various guidelines [27–30]. Monthly treatment till there is no edema on follow-up OCT scan and reinitiating treatment when edema recurs or vision deteriorates is the preferred clinical practice for the management of DME [30, 31].

However, according to the FDA label of Eylea® (aflibercept), 'the recommended dose for eylea (for DME) is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)' [32].

Cases that do not show a response after 3 monthly injections are termed non-responders [31]. Some authorities, however, term a patient nonresponder after the failure of 6 injections [29].

However, other definition of non-responder includes no or minimal reduction in retinal thickness on OCT or no improvement in visual acuity. The study by DRCR.net defined less than 10% decrease in central subfield thickness on OCT and < 5 letter increase in visual acuity as no response to anti-VEGF treatment [21]. Options to treat such cases include other anti-VEGF agents, intravitreal triamcinolone, implantable steroid injection, macular laser, and targeted retinal photocoagulation (TRP) of peripheral capillary nonperfusion areas [30, 31, 33].

Center-involved diabetic macular edema is defined as retinal thickening involving the central subfield zone of the macula that is 1 mm in diameter [34]. The management of center-involved macular edema causing visual decline (visual acuity worse than 20/30) is relatively straightforward and such cases need treatment [28, 35]. The preferred therapy includes intravitreal anti-VEGF agents, steroids, steroid implants, or a combination of these. Cases with center-involved macular edema and good visual function pose a challenge to the treating Ophthalmologist. The dilemma in such cases is whether to start intravitreal therapy or to observe [30, 34]. Such cases have been reported to improve with good control of blood sugar levels alone [31]. The role of anti-VEGF agents in such cases is being explored [36]. These cases have to be monitored at regular intervals to detect deterioration in vision which is an indication to begin anti-VEGF therapy [31, 34].

Non-center involved diabetic macular edema is defined as a retinal thickening in the macula that does not involve the central subfield zone of diameter 1 mm [34]. Laser photocoagulation is still the standard of care for the treatment of cases with non-center involving macular edema [37]. For cases with macular edema with vitreomacular traction, induction of posterior vitreous detachment during pars plana vitrectomy with or without ILM peeling is the recommended choice for treatment [38–40].

6. Biomarkers of DR on OCT

Biomarkers are markers used externally to assess a medical state reliably and accurately [41]. Biomarkers may be physical, chemical, or biological. They are used to assess a physiological state, pathological process, or response to any pharmacological intervention [41]. Imaging biomarkers have the advantage of being non-invasive, reliable, and accurate. Several OCT-based biomarkers have been reported in DME which help in the management of the disease as well as in prognostication [42].

6.1 Disorganization of the retinal inner layers (DRIL)

Earlier studies showed a variable correlation between central retinal thickness measured on OCT and visual acuity achieved post-treatment of DME [43, 44]. A study by DRCR.net revealed that this correlation is modest. They also documented cases with a paradoxical decrease in visual acuity with a decrease in retinal

thickening [45]. Further studies documented the role of OCT-based markers other than the central retinal thickness that affect visual acuity.

These include bridging retinal processes, the integrity of ELM and EZ, the reflectivity of cone outer segment tips, presence of hyperreflective foci, and subretinal fluid [46–49].

Long-standing cystoid macular edema with disturbance in ELM and EZ may suggest a poor visual outcome after treatment (**Figure 5**).

Sun and colleagues evaluated a novel marker in OCT, called disorganization of the retinal inner layers (DRIL), within the central 1 mm area of the fovea [50]. They studied the inner retinal layers in cases with existing DME or resolved DME. DRIL is 'defined as the horizontal extent in microns for which any boundaries between the ganglion cell–inner plexiform layer complex, inner nuclear layer, and outer plexiform layer could not be identified.' [50]. DRIL was found to have a substantial association with visual acuity. The presence of DRIL explained the paradoxical decrease in visual acuity in cases with resolved DME [50]. Later, Joltikov et al. reported the presence of DRIL in diabetics even before the presence of DR, DME, or PDR [51]. Further, Pelosini et al. proposed a theory to explain the negative correlation between retinal volume and visual acuity [52]. They suggested that the accumulation of fluid within the inner retinal layers causes the bipolar cells to stretch. Bipolar cells connect the photoreceptors to the ganglion cells. Fluid exceeding the limit of elasticity of these bipolar cell axons, may break the continuity of these axons and affect the transmission of signals between ganglion cells and photoreceptors. The irreversible destruction of bipolar cells provides a plausible explanation for cases with no improvement in visual acuity even after the resolution of DME [52]. In another study, the presence of retinal tissue between the cystic cavities in cases with DME was found to predict improvement in visual acuity after anti-VEGF therapy. These retinal tissues comprise of Müller and bipolar cells that transmit impulses between inner and outer retinal layers. The absence of these retinal bridging tissues at baseline explains the foveal thinning after the resolution of edema [53].

6.2 Hyperreflective retinal foci

SD-OCT imaging of diabetic retinopathy identified an additional intraretinal pathology which was visualized as hyperreflective dot or foci (HF) in few cases of DME [47]. Bolz et al. reported that the location of these HF on OCT was variable

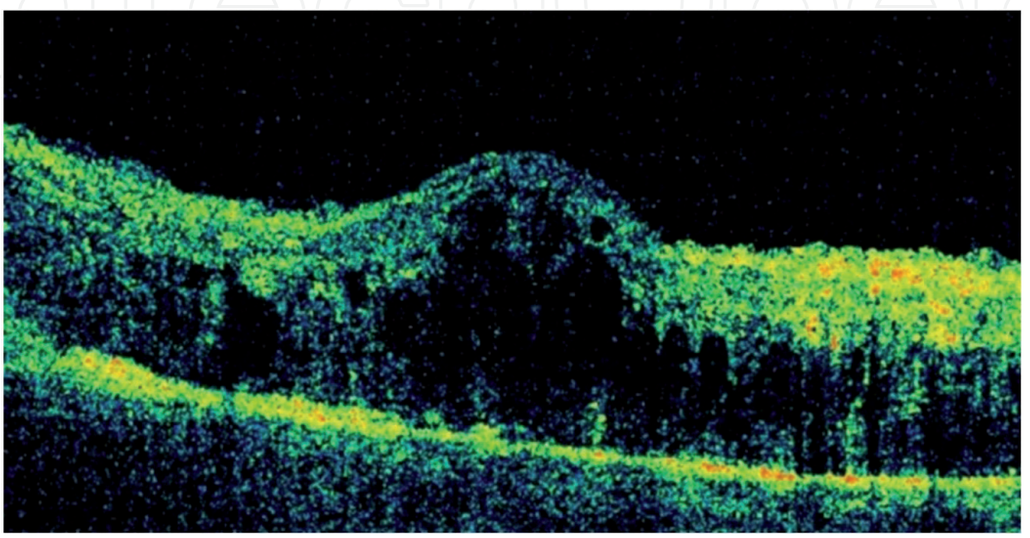

Figure 5.
Long standing cystoid macular edema.

[47]. In some cases, they were noted to be dispersed all through the retinal layers. In other cases, they were observed in the walls of microaneurysms or as confluent plaques at the level of the outer plexiform layer [47]. Bolz et al. hypothesized that the HF represented lipid deposits or precursors of hard exudates [47]. The similarity in the reflective property of HF and hard exudates supported their theory. In contrast, Lee and colleagues proposed that HF corresponded to activated microglial cells [54]. They observed a positive correlation between levels of the cytokine CD14 in the aqueous humor and the number of HF on SD-OCT in patients with DME. Cytokine CD14 is derived from activated microglial cells [55]. Microglial cells are the immune cells in the retina that undergo an inflammatory change in DR [56]. However, further studies are required to establish the origin of HF. Midena et al., described HF as dots with a size less than 30 microns, absence of back shadowing, and reflectivity similar to that of the retinal nerve fiber layer [57]. Their description allowed the distinction of HF from other hyperreflective spots on OCT such as intraretinal hemorrhage and microaneurysm. Intraretinal hemorrhage on OCT has a backshadowing effect such that retinal layers beneath the hemorrhage are not visualized. The microaneurysms on OCT have an external diameter of more than 70 microns in size [58]. Several studies reported a negative correlation between the presence of HF and visual acuity [59–62]. Uji et al. suggested a pathologic association between the presence of HF in the outer retinal layers and disruption of ELM and EZ resulting in photoreceptor dysfunction in cases with DME [59]. The presence of HF has been documented to indicate inflammatory activity or active disease status with studies reporting a significant reduction in HF after treatment with anti-VEGF and steroid implants [60, 61]. HF has also been identified as a predictor of early recurrence of DME after steroid (dexamethasone) implant [62]. HF has also been reported in DME cases that are refractory to anti-VEGF agents [63].

A characteristic arrangement of hyperreflective dots termed as pearl necklace sign in cases of DME was recently reported (**Figure 6**) [64]. It was originally described as HF surrounding the wall of a cyst located in the outer plexiform layer [64]. However, a similar appearance has recently also been described in cystoid spaces in the outer plexiform-outer nuclear layer and the inner wall of the neurosensory detachment [65]. Treatment with anti-VEGF agents in these cases led to the accumulation of hard exudates in the location of HF. A correlation of pearl necklace sign and visual acuity was only described in cases where the cyst or neurosensory detachment involved the fovea [65].

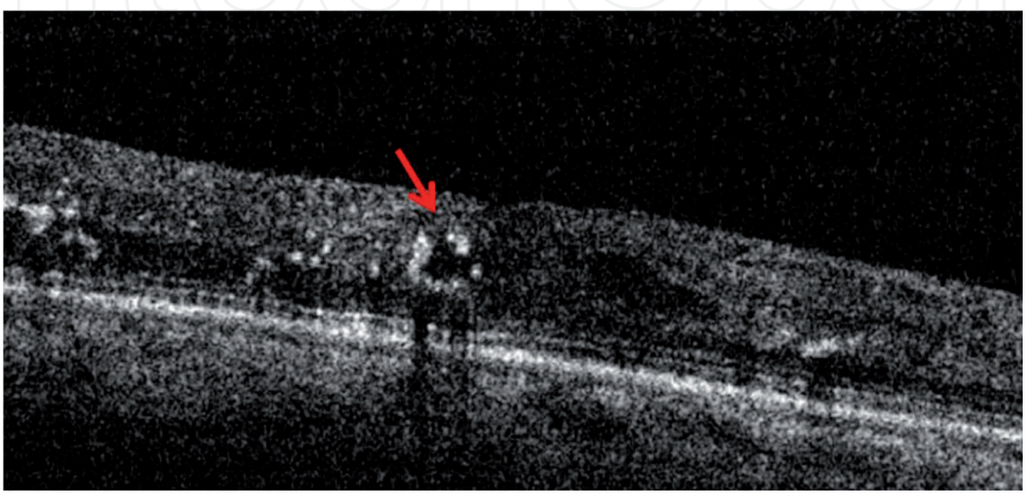

Figure 6.
Pearl necklace sign in a case of diabetic macular edema.

6.3 Hyperreflective material within intraretinal cystoid spaceSolid

Solid appearing cysts with hyper-reflective material within the cyst have been documented in DME (**Figure 7**) [66]. The content of these cysts has been hypothesized to be fibrin or of inflammatory origin [66]. However, no alteration to response to anti-VEGF treatment was reported [66].

Another novel OCT finding that has been recently reported in a patient with DME is a subretinal pseudocyst [67]. Contrary to what has been earlier documented, a cyst-like appearance was observed in the subretinal space and not within the retinal layers. The migration of Müller cells into the subretinal space has been proposed to be the reason for the development of the pseudocyst in that location [67].

6.4 Thickness of photoreceptor outer segment (PROS)

Advancement in technology has allowed the measurement of the thickness of the photoreceptor layer with SD-OCT in patients with diabetes. Patients with DR, DME, or diabetes but no retinopathy, have reported a thin photoreceptor layer in comparison to healthy individuals [46, 68]. Variation in visual acuity has been correlated to the thickness of the outer segment of the photoreceptor (PROS) in eyes with DME. This thickness of PROS is measured from the inner boundary of IS/OS junction to the inner boundary of the RPE layer [69]. The correlation of thickness of PROS with visual acuity is significant particularly when measuring it at the fovea [49].

6.5 Hyperreflective foci within the choroid

Hyperreflective foci within the choroid (HCF) have been recently reported in diabetic eyes [70]. Roy et al. hypothesized that these are intraretinal HF that migrate to the choroid with disruption of ELM and EZ. They documented a negative correlation between visual acuity and the presence of HF in the choroid. The presence of HCF was also observed to have an association with the severity of DR [70].

6.6 Thickness of the choroid

Studies using enhanced depth OCT imaging have evaluated choroidal thickness in eyes with DME and PDR. These studies have reported contradictory results. Kim and associates documented an increase in choroidal thickness with the increase in

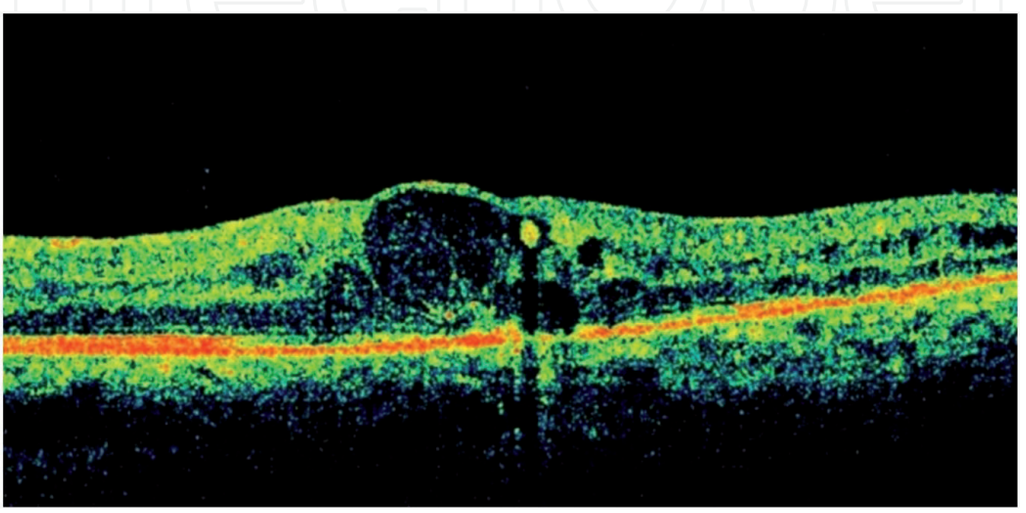

Figure 7.
Hyper reflective material within the cyst in a case of diabetic macular edema.

severity of DR and cases with DME [71]. They also reported a decrease in choroidal thickness in eyes treated with panretinal photocoagulation (PRP) [71]. In contrast, Querques et al. documented thin choroid in diabetic eyes when compared to control [72]. Rayess et al. documented that eyes with thicker choroid at baseline responded better to anti-VEGF treatment [73].

A recent study using swept-source OCT showed that choroidal thickness increased in the early stages of DR and then decreased as the severity of DR progressed [74]. The study proposed several mechanisms to explain choroidal thickening in early DR. Diabetic choroidopathy resulting in dysfunction of RPE and increased vascular permeability was implied as one of the mechanisms. Inflammation and oxidative stress-induced increase in cytokines was also suspected to be associated with choroidal thickening. In contrast, a decrease in blood flow and hypoxia was probably associated with thinning of the choroid with the progression of DR. However, whether choroidal thinning is primary or secondary to retinal ischemia remains to be established [74].

6.7 Choroidal vascularity index (CVI)

Choroidal vascularity index (CVI), another OCT-based marker enables the assessment of vascularity of the choroid [75]. Unlike choroidal thickness, this marker does not vary with physiological factors [75]. The choroid has two main components, the stroma, and the vascular layer. CVI is the proportion of the vascular component to the total choroidal area. A positive correlation has been documented between CVI and the status of choroidal blood supply [75]. Studies evaluating the CVI in diabetes have suggested that reduction in choroidal blood flow occurs as an early manifestation in diabetes even before retinopathy developed [76]. The thickening of choroid noted in the early stages of DR is probably explained by an increase in the stromal component of the choroid. As retinopathy progresses, the choroidal blood vessel further reduces in density [76]. However, further studies are required to confirm these theories.

7. Role of OCT in PDR

7.1 Neovascularization on OCT

High-resolution OCT imaging allows the evaluation of details of neovascularization in patients with PDR [77, 78].

Neovascularization of the retina was observed to breach the internal limiting membrane and protrude into the vitreous cavity [77]. The posterior hyaloid was attached or partially detached around the neovascularization [77]. Neovascular loops were seen as hyperreflective loops protruding into the vitreous with back-shadowing obscuring the retina at the points of attachment [77].

Thick neovascularization of the disc (NVD) was noted to grow along the posterior hyaloid which serves as a scaffold [77]. NVD appeared as hyperreflective tissue over the disc protruding into the vitreous cavity in cases with detached posterior hyaloid, which is uncommon in eyes with NVD [77]. Vaz-Pereira et al. in their study identified SD-OCT-based features that can distinguish active neovascularization from quiescent neovascularization [79]. They observed the presence of hyperreflective dots in the vitreous cavity in cases with active neovascularization. These hyperreflective dots were theorized to represent increased vascular permeability. Features such as the presence of epiretinal membrane, inner retinal tissue contracture, vitreous invasion, and protrusion towards the vitreous were found

in cases of quiescent or inactive neovascularization [79]. Another finding in PDR that is observed on OCT is vitreoschisis [80]. This is defined as the splitting of the posterior vitreous which leaves a layer of vitreous attached to the retina when vitreous detachment occurs. These can cause traction on the neovascular vessels and complicate surgery in PDR [80].

In contrast, intraretinal microvascular abnormalities (IRMA) are intraretinal, hyperreflective areas that were observed to distort the inner retinal layers. They do not breach the overlying ILM or vitreous. There is no thickening of the posterior hyaloid [77].

7.2 Wide-field OCT imaging in PDR

Mishra et al. have recently described a novel technique to facilitate wide-field imaging of the retina beyond the posterior pole. These images provide a better assessment of the vitreoretinal interface and therefore help in surgical planning in eyes with PDR [81].

8. Optical coherence tomography angiography (OCTA)

OCT angiography (OCTA) provides non-invasive imaging of the retinal vasculature parallel to images provided by FA [82]. The advantage over FA is that it circumvents the need for dye injection and therefore forestalls the risk of incidents like anaphylaxis. With the help of OCTA, people with contraindications to FA, can also undergo imaging of the retinal vasculature. OCTA uses the split-spectrum amplitude decorrelation algorithm [82]. In simple terms, it analyzes the light signals reflected from various tissues on repeated B scan imaging of a particular location. The mobile blood cells of the retinal or choroidal vasculature are the only structures responsible for providing a signal of different intensity or phases on repeated B scans [82]. The other tissues being stationary will not show any difference. It provides high-resolution images of both superficial and deep capillary plexus [83]. It provides better visualization of retinal capillary non-perfusion areas including capillary drop-out areas and foveal avascular zone [84]. Swept source-OCTA systems provide better imaging of the choroidal vasculature compared to SD-OCTA [85]. OCTA enables delineation of the morphology of microaneurysm into saccular or fusiform swelling [86]. Unlike FA, OCTA does not evaluate hyperpermeable pathological vessels. It does not show leakage (as seen on fundus fluorescein angiography) to indicate retinal edema or neovascularization [87]. OCTA also helps to estimate the activity status of the neovascularization [86]. Various quantitative measures have also been described using OCTA [88, 89]. Further details of OCTA are beyond the scope of this chapter.

9. Newer modalities in OCT

Adaptive optics OCT improves the transverse resolution of OCT images. Adaptive optics OCT provides microscopic images of the vasculature. It has been used to quantitatively analyze the lumen of retinal capillaries and microaneurysms in diabetic retinopathy [90, 91]. Based on the Doppler principle, Doppler OCT is a functional imaging technique that allows for visualization and measurement of blood flow [92]. Studies have observed reduced retinal blood flow in patients with DR compared to healthy individuals [93].

10. Conclusion

OCT has become a very valuable tool in the imaging of diabetic retinopathy. It is useful in the diagnosis of DME as well as decision-making regarding the treatment of DME. It is also helpful in following up the cases with DME after treatment with anti-VEGF therapy. It helps in diagnosing non-responders to treatment. It also provides information regarding the vitreoretinal interface and therefore helps decide the need for surgical intervention. It provides reliable qualitative information regarding retinal thickness. Various OCT-based classifications of DME have helped in better understanding of the disease pathogenesis. The evaluation of retinal layers on OCT explains the correlation between the retinal thickness at baseline and the final visual acuity achieved after treatment. The arrival of OCTA has further enhanced the imaging process. It adds to the information provided by SD-OCT or SS-OCT. It gives information regarding the blood supply of the retina, the density of the vessels, changes in the foveal avascular zone and helps to identify neovascular networks. It precludes the use of the invasive fundus fluorescein angiography and hence can be used in people with contraindications to fundus fluorescein angiography.

Thus, OCT has become a vital tool to diagnose and monitor the response of DME to various intravitreal pharmacotherapies including anti-VEGF agents.

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References

[1] Hou Y, Cai Y, Jia Z, et al. Risk factors and prevalence of diabetic retinopathy. Medicine (Baltimore). 2020 Oct 16;99(42):e22695.

[2] Thapa R, Bajimaya S, Sharma S, et al. Systemic association of newly diagnosed proliferative diabetic retinopathy among type 2 diabetes patients presented at a tertiary eye hospital of Nepal. Nepalese Journal of Ophthalmology. 2015 Sep 17;7(1):26-32.

[3] Wong TY, Sabanayagam C. Strategies to tackle the global burden of diabetic retinopathy: from epidemiology to artificial intelligence. Ophthalmologica. 2020;243(1):9-20.

[4] Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Archives of Ophthalmology 1984;102(4):527-532.

[5] Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. Ophthalmology. 1991 May 1;98(5):786-806.

[6] Diabetic Retinopathy Clinical Research Network. Reproducibility of macular thickness and volume using zeiss optical coherence tomography in patients with diabetic macular edema. Ophthalmology. 2007 Aug 1;114(8):1520-1525.

[7] Aumann S, Donner S, Fischer J, et al. Optical coherence tomography (OCT): Principle and technical realization. High Resolution Imaging in Microscopy and Ophthalmology. 2019:59-85.

[8] Chinn SR, Swanson EA, Fujimoto JG. Optical coherence tomography using a frequency-tunable optical source. Optics letters. 1997 Mar 1;22(5):340-342.

[9] Staurenghi G, Sadda S, Chakravarthy U, et al. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN•OCT consensus. Ophthalmology. 2014 Aug 1;121(8):1572-1578.

[10] Liu JJ, Witkin AJ, Adhi M, Grulkowski I, Kraus MF, Dhalla AH, Lu CD, Hornegger J, Duker JS, Fujimoto JG. Enhanced vitreous imaging in healthy eyes using swept source optical coherence tomography. PLoS One. 2014 Jul 18;9(7):e102950.

[11] Ishikawa H, Stein DM, Wollstein G, Beaton S, Fujimoto JG, Schuman JS. Macular segmentation with optical coherence tomography. Investigative ophthalmology & visual science. 2005 Jun 1;46(6):2012-2017.

[12] Otani T, Yamaguchi Y, Kishi S. Improved visualization of Henle fiber layer by changing the measurement beam angle on optical coherence tomography. Retina. 2011 Mar 1;31(3):497-501.

[13] Spaide RF, Curcio CA. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: literature review and model. Retina (Philadelphia, Pa.). 2011 Sep;31(8):1609.

[14] Spaide RF, Koizumi H, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. American journal of ophthalmology. 2008 Oct 1;146(4):496-500.

[15] Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. American journal of ophthalmology. 1999 Jun 1;127(6):688-693.

[16] Panozzo G, Parolini B, Gusson E, et al. Diabetic macular edema: an OCT-based classification. InSeminars inophthalmology 2004 Jan 1(Vol.19, No. 1-2, pp. 13-20). Taylor & Francis.

[17] Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. American journal of ophthalmology. 2006 Sep 1;142(3):405-412.

[18] Murakami T, Nishijima K, Sakamoto A, et al. Association of pathomorphology, photoreceptor status, and retinal thickness with visual acuity in diabetic retinopathy. American journal of ophthalmology. 2011 Feb 1;151(2): 310-317.

[19] Desislava Koleva-Georgieva. Optical Coherence Tomography Findings in Diabetic Macular Edema | IntechOpen [Internet]. 2021. Available from: https://www.intechopen.com/books/diabetic-retinopathy/optical-coherence-tomography-findings-in-diabetic-macular-edema

[20] Helmy YM, Allah HRA. Optical coherence tomography classification of diabetic cystoid macular edema. Clinical Ophthalmology(Auckland, NZ). 2013;7: 1731.

[21] Aiello LP, Beck RW, Bressler NM, et al. Rationale for the diabetic retinopathy clinical research network treatment protocol for center-involved diabetic macular edema. Ophthalmology. 2011 Dec 1;118(12):e5-14.

[22] Nguyen QD, Shah SM, Heier JS, et al. Primary end point (six months) results of the ranibizumab for edema of the macula in diabetes (READ-2) study. Ophthalmology. 2009 Nov 1;116(11): 2175-2181.

[23] Shah SM, Nguyen QD, Sy JP, et al. The RIDE and RISE studies of the efficacy and safety of intravitreal ranibizumab (LUCENTIS®) in clinically significant macular edema with center involvement secondary to diabetes mellitus. Investigative ophthalmology & visual science. 2008 May 14;49(13):1562–.

[24] Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photo-coagulation for diabetic macular edema. Ophthalmology. 2008 Sep 1;115(9): 1447-1459.

[25] Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology. 2012 Nov 1;119(11):2312-2318.

[26] Elman MJ, Ayala A, Bressler NM, et al. Intravitreal ranibizumab for diabetic macular edema with prompt vs. Deferred laser treatment: 5-year randomized trial results. Ophthalmology. 2015 Feb 1;122(2):375-381.

[27] Bakri SJ, Wolfe JD, Regillo CD, et al. Evidence-based guidelines for management of diabetic macular edema. Journal of VitreoRetinal Diseases. 2019 May;3(3):145-152.

[28] Chhablani J, Wong K, Tan GS, et al. Diabetic macular edema management in asian population: expert panel consensus guidelines. Asia-Pacific Journal of Ophthalmology. 2020 Sep 1;9(5):426-434.

[29] Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al. Guidelines for the management of diabetic macular edema by the european society of retina specialists (EURETINA). Ophthal-mologica. 2017;237(4):185-222.

[30] Hooper P, Boucher MC, Colleaux K, et al. Contemporary management of diabetic retinopathy in Canada: from guidelines to algorithm guidance. Ophthalmologica. 2014;231(1):2-15.

[31] Das T, Aurora A, Chhablani J, et al. Evidence-based review of diabetic macular edema management: Consensus statement on Indian treatment guidelines. Indian journal ofophthalmology. 2016 Jan;64(1):14.

[32] Eylea. Prescribing information. Regeneron Pharmaceuticals, Inc.; March 2021. Accessed April 21, 2021. https://www.regeneron.com/downloads/eylea_fpi.pdf.

[33] Takamura Y, Tomomatsu T, Matsumura T, Arimura S, Gozawa M, Takihara Y, Inatani M. The effect of photocoagulation in ischemic areas to prevent recurrence of diabetic macular edema after intravitreal bevacizumab injection. Investigative ophthalmology & visual science. 2014 Aug 1;55(8):4741-4746.

[34] Wong TY, Sun J, Kawasaki R, et al. Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology. 2018 Oct 1;125(10):1608-1622.

[35] Tripathy K, Raj Sharma Y, Chawla R, et al. Recent advances in management of diabetic macular edema. Current diabetes reviews. 2015 Jun 1;11(2):79-97.

[36] Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs. laser photocoagulation vs. observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. Jama. 2019 May 21;321(19):1880-1894.

[37] Scott IU, Danis RP, Bressler SB, et al. Effect of focal/grid photocoagulation on visual acuity and retinal thickening in eyes with non-center involved clinically significant diabetic macular edema. Retina (Philadelphia Pa.). 2009 May;29(5):613.

[38] Diabetic Retinopathy Clinical Research Network. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology. 2010 Jun;117(6):1087.

[39] Pendergast SD, Hassan TS, Williams GA, et al. Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid. American journal of ophthalmology. 2000 Aug 1;130(2):178-186.

[40] Yamamoto T, Akabane N, Takeuchi S. Vitrectomy for diabetic macular edema: the role of posterior vitreous detachment and epimacular membrane. American journal of ophthalmology. 2001 Sep 1;132(3):369-377.

[41] Biomarkers Definitions Working Group, Atkinson Jr. AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, Oates JA, Peck CC, Schooley RT, Spilker BA. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clinical pharmacology & therapeutics. 2001 Mar;69(3):89-95.

[42] Markan A, Agarwal A, Arora A, et al. Novel imaging biomarkers in diabetic retinopathy and diabetic macular edema. Therapeutic Advances in Ophthalmology. 2020 Sep;12:2515841420950513.

[43] Bandello F, Polito A, Borrello MD, et al. "Light" versus "classic" laser treatment for clinically significant diabetic macular oedema. British Journal of Ophthalmology. 2005 Jul 1;89(7):864-870.

[44] Ozdemir H, Karacorlu M, Karacorlu SA. Regression of serous macular detachment after intravitreal triamcinolone acetonide in patients with diabetic macular edema. American journal of ophthalmology. 2005 Aug 1;140(2):251-2e1.

[45] Diabetic Retinopathy Clinical Research Network. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology. 2007 Mar 1;114(3):525-536.

[46] Alasil T, Keane PA, Updike JF, et al. Relationship between optical coherence tomography retinal parameters and visual acuityin diabetic macular edema. Ophthalmology. 2010 Dec 1;117(12): 2379-2386.

[47] Bolz M, Schmidt-Erfurth U, Deak G, et al. Optical coherence tomographic hyperreflective foci. Ophthalmology. 2009 May 1;116(5):914-920.

[48] Deák GG, Bolz M, Ritter M, et al. A systematic correlation between morphology and functional alterations in diabetic macular edema. Investigative ophthalmology & visual science. 2010 Dec 1;51(12):6710-6714.

[49] Forooghian F, Stetson PF, Meyer SA, et al. Relationship between photoreceptor outer segment length and visual acuity in diabetic macular edema. Retina (Philadelphia Pa.). 2010 Jan;30(1):63-70.

[50] Sun JK, Lin MM, Lammer J, 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 Nov 1;132(11):1309-1316.

[51] Joltikov KA, Sesi CA, de Castro VM, et al. Disorganization of retinal inner layers (DRIL) and neuroretinal dysfunction in early diabetic retinopathy. Investigative ophthalmology & visual science. 2018 Nov 1;59(13):5481-5486.

[52] Pelosini L, Hull CC, Boyce JF, et al. Optical coherence tomography may be used to predict visual acuity in patients with macular edema. Investigative ophthalmology & visual science. 2011 Apr 1;52(5):2741-2748.

[53] Al Faran A, Mousa A, Al Shamsi H, et al. Spectral domain optical coherence tomography predictors of visual outcome in diabetic cystoid macular edema after bevacizumab injection. Retina. 2014 Jun 1;34(6):1208-1215.

[54] Lee H, Jang H, Choi YA, et al. Association between soluble cd14 in the aqueous humor and hyperreflective foci on optical coherence tomography in patients with diabetic macular edema. Investigative ophthalmology & visual science. 2018 Feb 1;59(2):715-721.

[55] Landmann R, Müller B, Zimmerli W. CD14, new aspects of ligand and signal diversity. Microbes and infection. 2000 Mar 1;2(3):295-304.

[56] Zeng HY, Green WR, Tso MO. Microglial activation in human diabetic retinopathy. Archives of ophthalmology. 2008 Feb 1;126(2):227-232.

[57] Midena E, Pilotto E, Bini S. Hyperreflective intraretinal foci as an oct biomarker of retinal inflammation in diabetic macular edema. Investigative ophthalmology & visual science. 2018 Nov 1;59(13):5366.

[58] Wang H, Chhablani J, Freeman WR, et al. Characterization of diabetic microaneurysms by simultaneous fluorescein angiography and spectral-domain optical coherence tomography. American journal of ophthalmology. 2012 May 1;153(5):861-867.

[59] Uji A, Murakami T, Nishijima K, et al. Association between hyperreflective foci in the outer retina, status of photoreceptor layer, and visual acuity in diabetic macular edema. American journal of ophthalmology. 2012 Apr 1;153(4):710-717.

[60] Vujosevic S, Berton M, Bini S, et al. Hyperreflective retinal spots and visual function after anti-vascular endothelial growth factor treatment in center-involving diabetic macular edema. Retina. 2016 Jul 1;36(7):1298-1308.

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

[62] Kim KT, Kim DY, Chae JB. Association between Hyperreflective Foci on Spectral-Domain Optical Coherence Tomography and Early Recurrence of Diabetic Macular Edema after Intravitreal Dexamethasone Implantation. Journal ofophthalmology. 2019 Nov 19;2019.

[63] Hwang HS, Chae JB, Kim JY, Kim DY. Association between hyperreflective dots on spectral-domain optical coherence tomography in macular edema and response to treatment. Investigative ophthalmology & visual science. 2017 Nov 1;58(13):5958-5967.

[64] 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 Oct 1;34(10): 2088-2095.

[65] Ajay K, Mason F, Gonglore B, et al. Pearl necklace sign in diabetic macular edema: Evaluation and significance. Indian journal of ophthalmology. 2016 Nov;64(11):829.

[66] Liang MC, Vora RA, Duker JS, et al. Solid-appearing retinal cysts in diabetic macular edema: a novel optical coherence tomography finding. Retinal Cases and Brief Reports. 2013 July 1;7(3):255-258.

[67] Sacconi R, Lutty GA, Mullins RF, et al. Subretinal pseudocysts: A novel OCT finding in diabetic macular edema. American journal of ophthalmologycase reports. 2019 Dec 1;16:100567.

[68] Özkaya A, Alkin Z, Karatas G, et al. Photoreceptor outer segment layer thickness measured manually on images from spectral domain optical coherence tomography in healthy volunteers. Journal français d'ophtalmologie. 2014 Jun 1;37(6):475-479.

[69] Ozkaya A, Alkin Z, Karakucuk Y, et al. Thickness of the retinal photoreceptor outer segment layer in healthy volunteers and in patients with diabetes mellitus without retinopathy, diabetic retinopathy, or diabetic macular edema. Saudi Journal of Ophthalmology. 2017 Apr 1;31(2):69-75.

[70] Roy R, Saurabh K, Shah D, et al. 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 Jul;8(4):314.

[71] Kim JT, Lee DH, Joe SG, et al. Changes in Choroidal Thickness in Relation to the Severity of Retinopathy and Macular Edema in Type 2 Diabetic Patients. Investigative ophthalmology & visual science. 2013 May 1;54(5): 3378-3384.

[72] Querques G, Lattanzio R, Querques L, et al. Enhanced depth imaging optical coherence tomography in type 2 diabetes. Investigative ophthalmology & visual science. 2012 Sep 1;53(10):6017-6024.

[73] Rayess N, Rahimy E, Ying G, et al. Baseline choroidal thickness as a predictor for response to anti–vascular endothelial growth factor therapy in diabetic macular edema. American journal of ophthalmology. 2015 Jan 1;159(1):85-91.

[74] Wang W, Liu S, Qiu Z, et al. Choroidal thickness in diabetes and diabetic retinopathy: a swept source OCT study. Investigativeophthalmology &visual science. 2020 Apr 9;61(4):29-29.

[75] Agrawal R, Gupta P, Tan K-A, et al. Choroidal vascularity index as a measure of vascular status of the choroid: Measurements in healthy eyes from a population-based study. Scientific Reports. 2016 Feb 12;6(1):1-9.

[76] Kim M, Ha MJ, Choi SY, et al. Choroidal vascularity index in type-2 diabetes analyzed by swept-source optical coherence tomography. Scientific Reports. 2018 Jan 8;8(1):70.

[77] Cho H, Alwassia AA, Regiatieri CV, et al. Retinal neovascularization secondary to proliferative diabetic retinopathy characterized by spectral domain optical coherence tomography. Retina (Philadelphia, Pa.). 2013 Mar;33(3):542-7.

[78] Pan J, Chen D, Yang X, et al. Characteristics of neovascularization in early stages of proliferative diabetic retinopathy by optical coherence tomography angiography. American journal ofophthalmology. 2018 Aug 1;192:146-156.

[79] Vaz-Pereira S, Zarranz-Ventura J, Sim DA, et al. Optical Coherence Tomography Features of Active And Inactive Retinal Neovascularization In Proliferative Diabetic Retinopathy. Retina. 2016 Jun 1;36(6):1132-1142.

[80] Vaz-Pereira S, Dansingani KK, Chen KC, et al. Tomographic relationships between retinal neovascularization and the posterior vitreous in proliferative diabetic retinopathy. Retina. 2017 Jul 1;37(7): 1287-1296.

[81] Mishra DK, Shanmugam MP, Ramanjulu R, et al. Comparison of standard and "innovative wide-field" optical coherence tomography images in assessment of vitreoretinal interface in proliferative diabetic retinopathy: A pilot study. Indian Journal of Ophthalmology. 2021 Jan;69(1):99.

[82] Spaide RF, Fujimoto JG, Waheed NK, et al. Optical coherence tomography angiography. Progress in retinal and eye research. 2018 May 1;64:1-55.

[83] Couturier A, Mané V, Bonnin S, et al. Capillary plexus anomalies in diabetic retinopathy on optical coherence tomography angiography. Retina. 2015 Nov 1;35(11):2384-2391.

[84] Soares M, Neves C, Marques IP, et al. Comparison of diabetic retinopathy classification using fluorescein angiography and optical coherence tomography angiography. British Journal of Ophthalmology. 2017 Jan 1;101(1):62-68.

[85] Choi W, Waheed NK, Molt EM, et al. Ultrahigh speed swept source optical coherence tomography angiography of retinal and choriocapillaris alterations in diabetic patients with and without retinopathy. Retina. 2017 Jan 1;37(1): 11-21.

[86] Ishibazawa A, Nagaoka T, Takahashi A, et al. Optical coherence tomography angiography in diabetic retinopathy: a prospective pilot study. American journal of ophthalmology. 2015 Jul 1;160(1):35-44.

[87] Hwang TS, Jia Y, Gao SS, et al. Optical coherence tomography angiography features of diabetic retinopathy. Retina (Philadelphia, Pa.). 2015 Nov;35(11):2371.

[88] Kim AY, Chu Z, Shahidzadeh A, et al. Quantifying microvascular density and morphology in diabetic retinopathy using spectral-domain optical coherence tomography angiography. Investigative ophthalmology & visual science. 2016 Jul 1;57(9):OCT362–OCT370.

[89] Chua J, Sim R, Tan B, et al. Optical Coherence Tomography Angiography in Diabetes and Diabetic Retinopathy. Journal of Clinical Medicine. 2020 Jun;9(6):1723.

[90] Jonnal RS, Kocaoglu OP, Zawadzki RJ, et al. A review of adaptive optics optical coherence tomography: technical advances, scientific applications, and the future. Investigative ophthalmology & visual science. 2016 Jul 1;57(9):OCT51–OCT68.

[91] Benesty J, Ayello-Scheer S, Sahel J, et al. Adaptive optics imaging of diabetic retinopathy. Investigative Ophthalmology & Visual Science. 2013 Jun 16;54(15):203.

[92] 92.Tan O, Jia Y, Wei E, Huang D. Clinical applications of Doppler OCT and OCT angiography. InOptical Coherence Tomography: Technology and Applications, Second Edition 2015 Jan 1 (pp. 1413-1428). Springer International Publishing.

[93] Srinivas S, Tan O, Nittala MG, et al. Assessment of retinal blood flow in diabetic retinopathy using Doppler Fourier-domain optical coherence tomography. Retina (Philadelphia, Pa.). 2017 Nov;37(11):2001.