Spectral Domain Optical Coherence Tomography Features and Classification Systems for Diabetic Macular Edema: A Review

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Abstract: Spectral domain optical coherence tomography (SD-OCT) is fast becoming the current standard of care for the detection and assessment of diabetic macular edema. With the application of SD-OCT for imaging of retinal microstructure and measurement of retinal thickness, new information regarding disease characteristics has been gathered, which was unrecognized previously. Retinal thickness measurements on SD-OCT have also been used for deciding the management and monitoring of the disease. Since its development, OCT has enhanced the understanding of retinal anatomical changes in diabetic retinopathy. Several authors have used SD-OCT to classify diabetic macular edema with the purpose of correlating the pathophysiology with disease severity. The classification systems have helped monitor the treatment efficacy and provide prognostic information on the treatment outcome. The following review article summarizes these classifications.

Key Words: diabetic retinopathy, diabetic macular edema, external limiting membrane, optical coherence tomography, photoreceptor inner segment ellipsoid zone

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The prevalence of diabetes mellitus is attaining epidemic proportions worldwide, with the number of people with diabetes mellitus expected to rise to 592 million by 2035.1 Diabetic retinopathy (DR) is associated with structural changes in the retina, with diabetic macular edema (DME) being the most common major cause of vision loss. Diabetic macular edema is characterized by a thickening of the macular region caused by breakdown in the inner and outer blood–retinal barrier (BRB) through loss of pericytes, microaneurysms, and dilated capillaries. Vascular endothelial growth factor (VEGF) is considered the main factor that disrupts BRB function. There are approximately 93 million people with DR and 21 million with DME in the world.2 According to studies on the natural history of DME, 24% of eyes with DME experienced visual loss of at least 3 lines of vision within 3 years.3

Optical coherence tomography (OCT) is a noninvasive, non-contact, transpupillary imaging modality that has become the current standard of care for the detection of DME. It has superseded the traditional and subjective tools like slit-lamp biomicroscopy, fluorescein angiography (FA),4,2 and stereo color fundus photography that were used to define clinically significant macular edema (CSME) by the Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group in 1991. Spectral domain OCT (SD-OCT) provides unparalleled high-resolution imaging with precise measurement of retinal thickness with high reproducibility and reliability. Both qualitative analysis based on the morphology and reflectivity profile of the retina along with quantitative analysis provide objective information for the detection of DME, allowing accurate follow-up for the progression of disease and evaluation of response to treatment.

CLASSIFICATION SYSTEMS OF DME

Diabetic macular edema has been classified on the basis of various parameters, including the presence of retinal thickening, hard exudates, location with relation to the fovea, morphological patterns of fluid accumulation, vitreomacular interface changes, quantitative analysis of fluid accumulation, and microstructural alteration in the retina. Various classifications have attempted to establish baseline variance in visual acuity, prognosticate the disease, rationalize treatment modality, and predict treatment outcomes. The published definitions of DME have been based on 4 examination methods including fundus biomicroscopy, color fundus photography, FA, and OCT.

On stereoscopic biomicroscopy, the ETDRS defined CSME as center and noncenter involving on the basis of the presence of retinal thickening and hard exudates.6 Diabetic macular edema with or without visual impairment should be considered for treatment when it fulfills the ETDRS criteria for CSME. Laser photocoagulation for DME mostly stabilizes the patient’s vision.7 Clinical trials of intravitreal anti-VEGF pharmacotherapies for the treatment of visual impairment due to center-involved DME observed an improvement or restoration of visual acuity in DME.8 A panel of experts recommended that current evidence for anti-VEGF treatment for DME should be based on involvement of the center of the macula.9 Laser photocoagulation based on ETDRS guidelines remains appropriate for the treatment of DME without center involvement, or for DME with center involvement without vision loss.9

The ETDRS Report Number 5 previously graded the proportion of leakage on FA from microaneurysms for classification of edema as focal or diffuse.10,11 With the availability of OCT, classification of DME based on FA is much less commonly used by clinicians. Clinical trials have used these classifications for comparing the treatment modalities of DR. The RESTORE and Diabetic Retinopathy Clinical Research Network (DRCR.net) studies relating to anti-VEGF monotherapy for DME observed no difference in visual outcome in the subgroup of focal and diffuse DME. The DRCR.net does not follow strict FA criteria for classification into focal or diffuse. Furthermore, the terms focal and diffuse DME are frequently used without clear definitions, and significant variations exist between different studies involving different examination methods.12
Several studies have correlated retinal sensitivity with visual acuity and retinal thickness at the fovea in patients with DME. Fundus-monitored microperimetry determines the retinal sensitivity, and retinal thickness is obtained by OCT. The retinal sensitivity within the central 2 and 10 degrees of the macula was observed to be significantly lower in eyes with DME in comparison with normal eyes. A negative correlation was found between retinal sensitivity and foveal retinal thickness. Retinal sensitivity supplements the predictive value of OCT in DME.

OCT-BASED MORPHOLOGICAL CLASSIFICATION SYSTEMS FOR DME

Otani et al proposed the first time domain OCT (TD-OCT) classification for DME based on retinal morphological changes in 1999 (Table 1). Accumulation of intraretinal fluid leads to increased retinal thickness and reduced reflectivity. They described 3 patterns of fluid accumulation as follows: sponge-like retinal swelling, cystoid macular edema, and serous retinal detachment. Initially, the fluid accumulates in the outer retinal layers, with further cystoid cavity formation correlating with histopathological finding of Muller cell necrosis. Persistent edema engages the inner retinal layers, leading to atrophy and appearance similar to retinoschisis. Serous retinal detachment was interpreted on OCT as detachment of the neurosensory retina with the presence of underlying fluid (nonreflecting space) above the hyperreflective line of the retinal pigment epithelium (RPE). Otani et al further observed a significant correlation between visual acuity and retinal thickness regardless of the different tomographic features. In 2004, Panozzo et al classified the morphological pattern in DME, taking into account the size of the cysts (Table 2).

In 2004, Kang et al correlated OCT and FA findings (focal leakage, diffuse, diffuse cystoid leakage) in DME and inferred a significant correlation between them. Kang et al classified DME

### Table 1. OCT-Based Morphological Classification of DME by Otani et al

<table>
<thead>
<tr>
<th>Type 1 (sponge-like swelling)</th>
<th>Thickening of the fovea with homogeneous optical reflectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 (cystoid macular edema)</td>
<td>Thickening of the fovea with markedly decreased optical reflectivity in outer layers</td>
</tr>
<tr>
<td>Type 3 (serous retinal detachment)</td>
<td>Thickening of the fovea with subfoveal fluid accumulation and distinct outer border of detached neurosensory retina</td>
</tr>
<tr>
<td>Type 3A</td>
<td>Without vitreofoveal traction</td>
</tr>
<tr>
<td>Type 3B</td>
<td>With apparent vitreofoveal traction</td>
</tr>
</tbody>
</table>

### Table 2. Classification of DME by Panozzo et al Based on Retinal Thickness, Volume, Morphology of Retina, and Macular Traction

<table>
<thead>
<tr>
<th>Retinal Thickness</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6.5 mm³ ± 1</td>
</tr>
<tr>
<td>Borderline</td>
<td>Up to 8.0 mm³</td>
</tr>
<tr>
<td>Edema</td>
<td>≥8.0 mm³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphology</th>
<th>E1</th>
<th>E2</th>
<th>E3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple: compact retinal thickening, no clinically visible cystoid spaces</td>
<td>Cystoid thickening: retinal thickening with cysts</td>
<td>Neuroepithelial detachment: isolated or associated with simple or cystoid retinal thickening</td>
<td></td>
</tr>
<tr>
<td><strong>E2A</strong></td>
<td><em>Mild</em>: 2–4 central small cysts each with horizontal diameter 150–200 μm, vertical diameter 400 μm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>E2B</strong></td>
<td><em>Intermediate</em>: cysts with petaloid configuration or central cysts with horizontal diameter less than 300 μm, vertical diameter less than 600 μm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>E2C</strong></td>
<td><em>Severe</em>: coalescence of cysts with appearance similar to retinoschisis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Epiretinal (Macular or Foveal) Traction (Tangential or Anteroposterior) |
|---------------------------|---------------------------|---------------------------|---------------------------|
| T0 | T1 | T2 | T3 |
| Absence of epiretinal hyperreflectivity | Presence of a continuous line of flat hyperreflectivity adherent to the retina without significant retinal distortion | Presence of continuous line of hyperreflectivity with multiple points of adhesion to the retina with distortion | Anteroposterior traction with “gull wings” configuration |

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www.apjo.org | 361
into 4 morphological types. Type 1 was described as thickening of the fovea with homogeneous optical reflectivity throughout the whole layer of the retina, whereas type 2 referred to thickening of the fovea with markedly decreased optical reflectivity in the outer retinal layers. Type 3 represented foveolar detachment without traction, and type 4 constituted foveolar detachments with apparent vitreofoveal traction. They observed that the morphological type of DME on OCT and the type of leakage on FA correlated with visual acuity. In 2008, Koleva-Georgieva and Sivkova classified DME in terms of the size of cystoid spaces and evaluated the progression of macular edema (Tables 3A and 3B). They found a correlation between the size of cystoid spaces, retinal thickness, and visual acuity. Recently, Helmy et al classified patients with cystoid macular edema into 4 groups based on the ratio of the vertical height of the largest macular cyst in relation to the maximum macular thickness, with the use of OCT (Table 4).

### QUANTITATIVE ANALYSIS OF DME ON OCT

Time domain OCT was widely used in clinical practice and was the principal instrument used in numerous studies conducted by the DRCR.net until 2011. Retinal thickness was measured as the value in microns of the distance between the OCT layers, the RPE, and the internal limiting membrane. The center point thickness was defined as the average of the thickness values at the intersection of the 6 radial scans of the fast macular thickness protocol. The central subfield was defined as the circular area enclosed by a circle of 6 mm diameter centered on the fovea.

### TABLE 3A. OCT-Based Classification of DME by Koleva-Georgieva and Sivkova

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Small cysts predominantly in the outer retinal layers</td>
</tr>
<tr>
<td>Moderate</td>
<td>Cysts mainly located in the outer layers</td>
</tr>
<tr>
<td>Severe</td>
<td>Cysts mainly located in the outer layers predominantly in the fovea</td>
</tr>
</tbody>
</table>

### TABLE 3B. Classification by Koleva-Georgieva With Retinal Thickness, Morphology, Topography, Presence and Severity of Macular Traction, and Photoreceptor Inner Segment EZ Integrity

<table>
<thead>
<tr>
<th>Retinal Thickness</th>
<th>Early Subclinical Macular Edema</th>
<th>Established Macular Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Macular Edema</td>
<td>No clinically detected retinal thickening on ophthalmoscopy, OCT measured retinal thickness exceeding normal + 2 SD for central fixation point and fovea</td>
<td>Retinal thickening and evident morphological characteristics of edema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Retinal Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Nocystoid Macular Edema</td>
</tr>
</tbody>
</table>

- Increased retinal thickness, intraretinal reduced reflectivity, irregularity of the layered structure, flattening of the foveal depression without presence of cystoid spaces

<table>
<thead>
<tr>
<th>Cystoid Macular Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Mild: cystoid spaces with horizontal diameter &lt; 300 μm</td>
</tr>
<tr>
<td>(b) Intermediate: cystoid spaces with horizontal diameter of 300–599 μm</td>
</tr>
<tr>
<td>(c) Severe: cystoid spaces with horizontal diameter ≥ 600 μm, or large confluent cavities with retinoschisis appearance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serous Macular Detachment</th>
</tr>
</thead>
</table>

- CSME, as defined by ETDRS and evaluated on the OCT retinal topography map

### TABLE 4. SD-OCT–Based Classification of DME by Helmy et al

| CME I                      | Cysts less than 30% of macular thickness                   |
| CME II                     | Cysts between 30% and 60% of macular thickness            |
| CME III                    | Cysts between 60% and 90% of macular thickness            |
| CME IV                     | Cysts more than 90% of the macular thickness              |
| A                         | Cysts without any disruption to the ELM or EZ             |
| B                         | Cysts with ELM disruption                                 |
| C                         | Cysts with EZ disruption                                  |
| D                         | Cysts with disruption of both the ELM and EZ              |

CME indicates cystoid macular edema.

**Koleva-Georgieva DN. Optical coherence tomography findings in diabetic macular edema. In: Ola MS, ed. Diabetic Retinopathy. Vienna, Austria: InTech; 2012. ERM indicates epiretinal membrane; PVD, posterior vitreofoveal detachment.**
Spectral domain OCT has subsequently and Kim
In the recently published DRCR.net
Disruptions of these
Center point thickness or CST
studied the role of traction and defined 3
(Table 5) also considered the presence of vitreofoveal trac-
The presence of vitreoretinal trac-
www.apjo.org
In a clinical setting, an additional 10% measure-
The postop-
Volume 5, Number 5, September/October 2016
later put forward a classifica-
The group defined vitreo-
However, baseline
Protocol T, central subfield thickness (CST) was used as a major
criterion for determining treatment eligibility. A reference limit
of at least 250 \( \mu \)m thickness on Stratus (Carl Zeiss Meditec) was
one of the key inclusion criteria. The recommended equivalent
values were 320 \( \mu \)m or greater for men or 305 \( \mu \)m or greater for
women on Spectralis (Heidelberg Engineering) and 305 \( \mu \)m or
greater for men or 290 \( \mu \)m or greater for women on Cirrus (Carl
Zeiss Meditec).\(^\text{21}\) In a clinical setting, an additional 10% measurement
error should be adjusted for change in instrument before
evaluating the change in retinal thickness for monitoring progression
or efficacy of treatment.\(^\text{22}\) Center point thickness or CST measured by OCT has been observed to be modestly correlated
with visual acuity. This suggests the role of additional factors like
glycated hemoglobin, age, and other retinal structural alterations
to be responsible for variation in visual acuity at baseline and
follow-up after focal laser photocoagulation.\(^\text{24}\) However, baseline
CST values have been shown to correlate with visual acuity outcomes
after anti-VEGF therapy. Central subfield thickness less than 300 \( \mu \)m had lower gains in vision with ranibizumab in comparison with those with thicker baseline CST values.\(^\text{25}\) The
DRCR.net Protocol I study also documented that patients with
poor baseline visual acuity or CST greater than 400 \( \mu \)m experienced more visual gain.\(^\text{26}\)
Retinal thickness and volume were also taken into consideration
by Panozzo et al\(^\text{16}\) in their classification system (Table 2). Kang et al\(^\text{17}\) and Kim
et al\(^\text{34}\) (Table 5) also considered the presence of vitreofoveal traction in their classifications. Koleva-Georgieva and Sivkova\(^\text{27,28}\)
took into account the presence or absence of posterior vitreous detachment, presence of epiretinal membrane, and its effect on the
surface of the retina (Table 3B). Studies have now established a beneficial role of vitrectomy in improving the anatomical and visual outcomes in DME.\(^\text{30}\)

### PHOTORECEPTOR ELLIPSOID ZONE DISRUPTION ANALYSIS

Spectral domain OCT has enabled the visualization of integrity of the outer retinal layers, the photoreceptor external limiting membrane (ELM), and inner segment ellipsoid zone. Lu et al\(^\text{18}\) suggested that the inner segment ellipsoid zone (EZ) of the photoreceptors corresponds to the highly reflective band of the IS/OS junction seen on OCT. An expert panel introduced the term “zone” as a consensus nomenclature for anatomic regions like the photoreceptor inner segment EZ, which lacks definitely proven evidence for a specific reflective structure on OCT.\(^\text{36}\) Disruptions of these layers have been associated with increased severity of DR.\(^\text{37}\) Several authors have also found a positive correlation of visual acuity with the integrity of the EZ and ELM.\(^\text{38–40}\) The postoperative status of the photoreceptors has also been correlated to the final visual outcome after resolution of normal retinal morphology after surgery (Fig. 1).\(^\text{41}\)

| TABLE 5. Classification of DME by Kim et al\(^\text{34}\) |
|-----------------|----------------------------------|
| Type 1          | Diffuse retinal thickening       |
| Type 2          | Cystoid macular edema            |
| Type 3          | Serous retinal detachment without PHT |
| Type 4          | PHT without TRD                  |
| Type 5          | PHT with TRD                     |

PHT indicates posterior hyaloid traction; TRD, traction retinal detachment.

1 mm in diameter centered around the center point. The central subfield mean thickness was defined as the mean value of the 128 thickness measurements obtained in this circular area. Absolute change in retinal thickness was defined as the difference in the thickness obtained at 2 different times. The absolute change in thickness divided by baseline thickness provides the relative change in thickness.\(^\text{70}\) Spectral domain OCT has subsequently widely replaced TD-OCT. Spectral domain OCT machines generate higher retinal thickness values relative to TD-OCT machines. The median difference between TD-OCT and SD-OCT is estimated to be 43 to 67 \( \mu \)m.\(^\text{21}\) In the recently published DRCR.net Protocol T, central subfield thickness (CST) was used as a major criterion for determining treatment eligibility. A reference limit of at least 250 \( \mu \)m thickness on Stratus (Carl Zeiss Meditec) was one of the key inclusion criteria. The recommended equivalent values were 320 \( \mu \)m or greater for men or 305 \( \mu \)m or greater for women on Spectralis (Heidelberg Engineering) and 305 \( \mu \)m or greater for men or 290 \( \mu \)m or greater for women on Cirrus (Carl Zeiss Meditec).\(^\text{25}\) In a clinical setting, an additional 10% measurement error should be adjusted for change in instrument before evaluating the change in retinal thickness for monitoring progression or efficacy of treatment.\(^\text{22}\) Center point thickness or CST measured by OCT has been observed to be modestly correlated with visual acuity. This suggests the role of additional factors like glycated hemoglobin, age, and other retinal structural alterations to be responsible for variation in visual acuity at baseline and follow-up after focal laser photocoagulation.\(^\text{24}\) However, baseline CST values have been shown to correlate with visual acuity outcomes after anti-VEGF therapy. Central subfield thickness less than 300 \( \mu \)m had lower gains in vision with ranibizumab in comparison with those with thicker baseline CST values.\(^\text{25}\) The DRCR.net Protocol I study also documented that patients with poor baseline visual acuity or CST greater than 400 \( \mu \)m experienced more visual gain.\(^\text{26}\)

Retinal thickness and volume were also taken into consideration by Panozzo et al\(^\text{16}\) in their classification system (Table 2). Kang et al\(^\text{17}\) and Kim
et al\(^\text{34}\) (Table 5) also considered the presence of vitreofoveal traction in their classifications. Koleva-Georgieva and Sivkova\(^\text{27,28}\)
took into account the presence or absence of posterior vitreous detachment, presence of epiretinal membrane, and its effect on the
surface of the retina (Table 3B). Studies have now established a beneficial role of vitrectomy in improving the anatomical and visual outcomes in DME.\(^\text{30}\)

### VITREOMACULAR INTERFACE ANALYSIS

Recently, the International Vitreomacular Traction Study Group developed an OCT-based anatomic classification system for diseases of the vitreomacular interface.\(^\text{79}\) The group defined vitreomacular adhesion as perifoveal vitreous separation with remaining vitreomacular attachment and undisturbed foveal morphologic features. Vitreomacular traction is characterized by anomalous posterior vitreous detachment accompanied by anatomic distortion of the fovea. A number of published studies have postulated the role of tangential traction exerted by the posterior hyaloid on the retinal surface in DME.\(^\text{30,31}\) The presence of vitreoretinal traction in treatment unresponsive DME is an indicator for surgical intervention. In addition to relief of traction, other theories such as improved transvitreal oxygenation of the retina and removal of a growth factor reservoir in the premacular hyaloid have been postulated for improved retinal structure and function after vitrectomy.\(^\text{32,33}\)

Panozzo et al\(^\text{16}\) studied the role of traction and defined 3 types of epiretinal membranes (Table 2). Kang et al\(^\text{17}\) and Kim
et al\(^\text{34}\) (Table 5) also considered the presence of vitreofoveal traction in their classifications. Koleva-Georgieva and Sivkova\(^\text{27,28}\)
took into account the presence or absence of posterior vitreous detachment, presence of epiretinal membrane, and its effect on the
surface of the retina (Table 3B). Studies have now established a beneficial role of vitrectomy in improving the anatomical and visual outcomes in DME.\(^\text{30}\)

### FIGURE 1. Spectral domain optical coherence tomography showing grades of disruption of the ELM and EZ. A, Grade 0: no disruption of ELM and EZ. B, Grade 1: ELM disruption (white arrow), EZ intact. C, Grade 2: both ELM and EZ disrupted (yellow arrow).
Maheshwary et al graded the severity of EZ disruption in eyes with DME in 2010. Grades from each patient’s horizontal and vertical SD-OCT scans were added to yield a global disruption scale (Table 6). The percentage of disruption along the EZ band, measured 500 μm in either direction from the foveal center, was recorded. They demonstrated that the percentage of disruption of the photoreceptor EZ band was an important predictor of visual acuity in patients with DME. Sharma et al in 2014 gave a simplified, comprehensive, and physician-friendly approach to grading EZ disruption based on SD-OCT findings (Table 7). The EZ was studied using horizontal and vertical SD-OCT views through the fovea. The study also illustrated a significant decrease in visual acuity correlated with an increase in the grade of disruption of the EZ in patients with DR, and a marked decrease in visual acuity was found to be associated with global disruption.

In 2013, Jain et al showed for the first time that ELM disruption occurred earlier than disruption of the EZ (Table 8, Fig. 1). This was based on the observation that the ELM has tight junctions similar to those between RPE cells. Therefore, the ELM acts like the third outer BRB and its disruption contributes to fluid accumulation in DME. The disruption of the EZ is secondary to disrupted ELM. This was observed in experimental mice where a mutation leading to disruption of the ELM was found to cause shortening of the photoreceptor inner segment. A significant positive correlation was found between logMAR visual acuity and grade of disruption. Helmy et al also took into consideration the presence of photoreceptor ELM and EZ disruption in their classification of DME (Table 4). In another study, Murakami et al overcame the limitation of variability in the reflectivity levels of continuous EZ bands seen on SD-OCT. Relatively homogeneous and continuous ELM bands were described as intact, whereas absent or discontinuous ELM bands were described as disrupted. Quantification of the status of the transverse length of each segment of disrupted EZ and ELM band was performed. Statistical analysis demonstrated that the total additive transverse length of disrupted EZ and ELM within the fovea correlated more closely with logMAR visual acuity than did foveal thickness measurements.

Classifications based on OCT have proved to be useful in monitoring disease progression and in clinical trials for the treatment of DME. Trials on anti-VEGF have recommended the initiation of anti-VEGF therapy for foveal center-involving DME with visual impairment but laser photocoagulation for noncenter-involving cases. Vitrectomy for DME has been found to have good visual outcome in cases with traction over the retina.

### TABLE 6. SD-OCT-Based Classification of Retinal Photoreceptor Inner Segment EZ Disruption in Diabetes Mellitus by Maheshwary et al

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Intact EZ</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Focal disruption (localized, subfoveal EZ disruption)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Global disruption (generalized EZ disruption</td>
</tr>
<tr>
<td></td>
<td>throughout the macular cube)</td>
</tr>
</tbody>
</table>

At present, clinical decision making about DME management is mostly based on simple qualitative evaluation of baseline and follow-up OCT scans and thickness measurements. Various previously mentioned physician-friendly classification systems provide in vivo retinal structural alterations with regard to pathophysiology of the disease process. These structural alterations correlate with changes in visual acuity. These classification systems provide a systematic approach to the diagnosis and management of DME and are useful for execution and analysis of clinical studies. The recent focus has been on outer retinal structural alterations and integrity of inner retinal layers. Changes in these parameters correlate with changes in visual acuity and facilitate treatment decision making.

### MACULAR ISCHEMIA IN DME

Macular ischemia has been suggested to be associated with poor visual outcomes in patients with DME. Studies have documented macular ischemia to have a limiting effect on visual outcomes after intravitreal bevacizumab injections in patients with DME.

Fluorescein angiography has been used to identify macular ischemia. The size of the foveal avascular zone (FAZ) and its outline, on FA, correspond to the ischemic state of the macula. Several recent reports suggested that OCT can detect the structural changes in the retina due to ischemic changes. Byeon et al assessed foveal ganglion cell layer damage in ischemic diabetic maculopathy and postulated that OCT provides objective results and might be a good noninvasive substitute for FA. Further studies documented a significant correlation of ganglion cell layer damage with duration of diabetes. In patients with severe nonproliferative and proliferative DR without DME, no significant association of FAZ outline or size was found with retinal volume, total retinal thickness, and thickness of the outer and inner retina and ganglion cell layer. There is a contradictory association between the FAZ outline and continuity of the ELM and EZ. Certain studies mention foveal ischemia in DME to cause EZ disruption resulting in outer retinal layer atrophic changes and subsequent visual loss. Studies correlating choroidal thickness and FAZ enlargement in patients with DME have also documented contradictory results.

In most of the OCT studies in DR, the effects of macular ischemia are masked by coexisting DME. Fluorescein angiography remains the gold standard for evaluating the retinal perfusion status and for detecting macular ischemia in patients with DR. Recently, OCT angiography was found to be useful for quantifying retinal ischemia in diabetic DR. The paravascular and perifoveal vessel density are significantly reduced and low-perfusion areas are significantly increased in eyes with DR. Areas of low perfusion in OCT angiogram corresponded to ischemic areas in FA.

### HYPERREFLECTIVE SPOTS

Bolz et al described the distribution of hyperreflective spots throughout all the retinal layers in eyes with DME. They hypothesized that the hyperreflective spots represent subclinical features
of lipoprotein extravasation that act as precursors of hard exudates.\(^5\) Uji et al documented that the hyperreflective spots were located in the outer retina and were closely associated with disruption of the ELM and EZ. The hyperreflective spots were also associated with decreased visual acuity. Further, the degenerated photoreceptors were suggested to give origin to the hyperreflective spots.\(^5\) Framme et al reported the presence of hyperreflective spots in patients with both focal and diffuse DME. After anti-VEGF pharmacotherapy, the hyperreflective spots were found to reduce significantly. Therefore, the hyperreflective spots were hypothesized to represent clinical markers of inflammatory response.\(^5\) Recent studies, including experimental studies, have documented the location of hyperreflective spots in the inner retinal layers. These were found at an early stage of DR with absence of macular edema or hard exudates. These hyperreflective spots were even present in the eyes of patients with diabetes without retinopathy. The hyperreflective spots are hypothesized to represent the activation of retinal microglia located in the inner retinal layers. Microglial cells on activation undergo significant changes in shape and size and form microglial aggregates. Further, the number of hyperreflective spots increases with the clinical progression of DR and shows an inner to outer retina migration.\(^5\)

**BIOMARKERS FOR DME**

Biomarkers are a subcategory of medical signs that objectively indicate the state of health and wellbeing of an individual. These can be anatomical, biochemical, and molecular parameters or imaging features. In clinical practice, they are useful in refinement of diagnosis, measuring disease progression, or predicting and monitoring the effects of therapeutic interventions. The availability of biomarkers of DR progression offers new perspectives for understanding DR.\(^6\) Cunha-Vaz et al\(^6\) identified microaneurysms as a biomarker of development of CSME, with subclinical macular edema identified by OCT and multifocal electroretinogram as organ-specific biomarkers of DR. Nunes et al identified 3 different phenotypes of diabetes on the basis of the formation and disappearance of microaneurysms, presence of capillary closure, and alteration of the BRB with associated retinal edema. These different phenotypes were associated with different risks for progression of DR and development of CSME.\(^5\) Recently, OCT-based macular thickness parameters, cube average thickness and CST, were observed to be potential imaging biomarkers for DME.\(^5\) They serve as indicators of progression of disease within the grade of retinopathy.\(^6\) Sharma et al\(^6\) documented the role of nitric oxide and oxidative stress markers like lipid peroxide as indicators of in vivo structural alteration in the retinal photoreceptor EZ. Recently, Saxena et al\(^6\) documented the serum levels of urea and creatinine as surrogate markers for disruption of the retinal photoreceptor ELM and EZ observed on SD-OCT in DR.

**CONCLUSIONS**

To summarize, SD-OCT is an established imaging modality that has made a significant impact in the diagnostic evaluation of patients with DME. It helps in understanding the anatomy and pathophysiology of DME. However, currently there is no internationally accepted, standardized SD-OCT–based classification for DME. This probably reflects the complexity of the changes in DME and the wide range of findings and clinical implications. However, careful study of certain SD-OCT–based changes may demonstrate the sequence of events with the progression of disease and can guide decision making regarding the initiation, continuation, or interruption of therapy. Understanding disease with the assistance of OCT has helped in choosing the treatment modality, whether medical or surgical. With various clinical trials on anti-VEGF pharmacotherapy, SD-OCT has become an indispensable tool in clinical practice.

**REFERENCES**


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Everything you see or hear or experience in any way at all is specific to you. You create a universe by perceiving it, so everything in the universe you perceive is specific to you.

— Douglas Adams