

# The use of optical coherence tomography in the assessment of diabetic retinopathy and maculopathy

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The authors have no proprietary interest in the devices used. This study was conducted in accordance to the Declaration of Helsinki.

## Abstract

This review was performed to assess the use of optical coherence tomography in diabetic retinopathy and maculopathy and its application in the diagnosis and management of these conditions. A comprehensive literature search on MEDLINE was performed for studies published until 2013 with key words 'diabetes mellitus', 'optical coherence tomography', 'diabetic retinopathy', 'diabetic maculopathy', 'intersessional repeatability', 'diurnal variation', 'fundus autofluorescence' and 'treatment'. Search results were limited to studies published in English and in human subjects only. The Early Treatment Diabetic Retinopathy Study established the current standard of care for diabetic retinopathy and maculopathy with the diagnosis based on slit-lamp biomicroscopy, indirect ophthalmoscopy, and fluorescein angiography. There has been a recent

shift to the use of optical coherence tomography in the qualitative and quantitative assessment of such diseases. Furthermore, the advancement of optical coherence tomography from time-domain to spectral-domain technology allows us to visualize pathological changes of diabetic maculopathy in details in different retinal layers. Such observed changes have been used to establish new classifications of diabetic maculopathy. The high sensitivity and quantitative nature of optical coherence tomography make it a highly popular modality used extensively to monitor disease progression and efficacy of new treatment modalities. Optical coherence tomography plays a crucial role in the modern clinical management of diabetic retinopathy and maculopathy. Its use has revolutionized the understanding and management of these eye diseases.

**Key words:** Diabetic retinopathy; Macular degeneration; Tomography, optical coherence



## Introduction

The current standard of care for diabetic retinopathy was established by the Early Treatment Diabetic Retinopathy Study (ETDRS) conducted in the late 1980s.<sup>1,2</sup> Diagnosis was mainly based on slit-lamp biomicroscopy, indirect ophthalmoscopy, and fundus fluorescein angiography (FFA).<sup>3</sup> However, these clinical findings are subjective and the assessments are difficult to quantify objectively. Since the introduction of optical coherence tomography (OCT) in 1995,<sup>4,7</sup> it has quickly been incorporated into the daily management of retinal diseases.<sup>8,9</sup> Recent advances in OCT technology improved our understanding of the anatomy of the retina in diabetic retinopathy and pathogenesis of the condition, and also revolutionized the diagnosis and management of this blinding disease.<sup>8</sup>

In a recent randomized controlled trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), OCT measurements of macular thickness were adopted as primary monitoring parameters in the management of patients with diabetic maculopathy.<sup>3</sup> This established the vital role of OCT in the modern management of diabetic retinopathy. This review provides up-to-date information regarding the use of OCT in diabetic retinopathy.

## Methods

A comprehensive literature search on MEDLINE was performed for studies published until 2013 with key words 'diabetes mellitus', 'optical coherence tomography', 'diabetic retinopathy', 'diabetic maculopathy', 'intersession repeatability', 'diurnal variation', 'fundus autofluorescence' and 'treatment'. Search results were limited to studies published in English and in human subjects only. Selected papers were then reviewed thoroughly and evidence was summarized.

## What is optical coherence tomography?

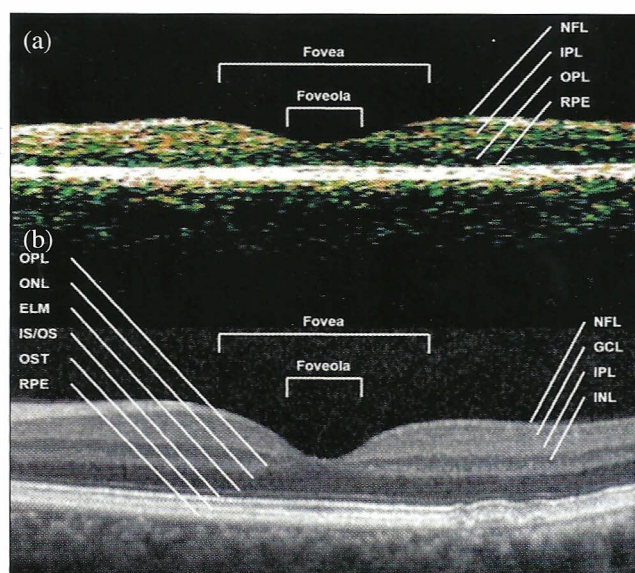
OCT is a non-contact and non-invasive imaging modality used to perform high-resolution, cross-sectional imaging. Images obtained by OCT are finer than those obtained by conventional imaging technologies such as ultrasound, magnetic resonance imaging or computed tomography. It allows both qualitative assessment of the retinal contour and quantitative measurement of retinal thickness.

## Principles of optical coherence tomography

OCT utilizes interferometry to acquire high-resolution in-vivo retinal images. Infrared light is projected onto the retina (A-scans), and reflectance data from backscattered light are interpreted. This is similar to the principle of ultrasonography except that OCT utilizes light wave (with much shorter wavelength of 700-800 nanometers) resulting in a much higher resolution. The retinal nerve fiber layer thickness can be calculated using automated segmentation algorithm. A cross-sectional image of the retina can be reconstructed

by combining data from a series of side-by-side A-scans.<sup>4,5</sup> The widely available Stratus OCT, a third-generation OCT instrument produced by Carl Zeiss Meditec (Dublin [CA], USA), utilizes 'Time' domain technology, where data from a moving reference mirror within the machine are compared with the interference pattern generated by echo time delays of backscattered light from the subject's retina.<sup>10-12</sup> By this method, the Stratus OCT gives an axial resolution of 8 to 10 microns and a scan speed of 400 A-scans per second. Using different scanning protocols, images focusing on the macula, optic disc and areas of particular interest can be interpreted. In-vivo pre-retinal, intra-retinal and sub-retinal anatomy and pathology can be delineated to aid clinical decisions.<sup>8</sup>

Recently, several manufacturers have developed a new generation of OCT utilizing the 'Spectral' domain technology, which is also known as the 'Fourier domain' OCT. Examples include Cirrus Spectral-domain OCT (Carl Zeiss Meditec; Dublin [CA], USA), Nidek RS-3000 OCT (Nidek Co. Ltd., Gamagori, Aichi, Japan), Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and Topcon 3D OCT-2000 (Topcon Corporation, Japan). The Spectral-domain technology does not require a reference mirror and does not measure reflectivity of each A-scan at a time. Instead, the spectrometer senses the relativity of multiple



**Figure 1.** Optical coherence tomography scan through a normal central fovea.

(a) Image acquired using time-domain OCT (Stratus OCT, Carl Zeiss Meditec, USA); (b) Image acquired in same patient using spectral-domain OCT (Spectralis OCT, Heidelberg Engineering, USA). Note the higher resolution. Different layers within the retina can be clearly seen.

Abbreviations: ELM = external limiting membrane; GCL = ganglion cell layer; INL = inner nuclear layer; IPL = inner plexiform layer; IS/OS = photoreceptor inner segment/outer segment; NFL = nerve fiber layer; OCT = optical coherence tomography; ONL = outer nuclear layer; OPL = outer plexiform layer; OST = photoreceptor outer segment tip; RPE = retinal pigment epithelium.



optical frequencies simultaneously from the backscattered light. Thus, many sample points can be measured at the same time allowing up to 100 times faster scanning acquisition speed. This new generation of OCT is able to produce axial resolution of 5 microns and a scan speed of up to 40,000 A-scans per second. Collected data are calculated using Fourier transformation. This allows imaging of the retina at much greater precision.<sup>13-15</sup> Normal OCT cross-section of the foveal region is shown in **Figure 1**. With the improved technology, a 3-dimensional image of the in-vivo retina can also be produced.

Advantages of optical coherence tomography

Quantifying retinal thickness

A major advantage of OCT is its ability to quantify retinal thickness.<sup>8</sup> The assessment of retinal status by traditional imaging modalities is subjective and qualitative. In comparison, retinal thickness measured by OCT can be quantified in terms of microns, and mapped out according to the topographic data obtained. Quantification of retinal thickness is made possible by calculating the distance between the anterior and posterior highly reflective interfaces of the retina. The anterior interface (the internal limiting membrane) is well defined on OCT due to its contrast with the non-reflective vitreous. The posterior border (the retinal pigment epithelium) is well defined on OCT as the first signal posterior to the low-scattered photoreceptor layer.<sup>5</sup> Quantification of retinal thickness by OCT provides more accurate monitoring and documentation of disease progression than with traditional imaging modalities.

Non-invasiveness and convenience

OCT measurements are taken easily with the patients sitting and resting their head on the chin-rest of the machine. Unlike ultrasound biomicroscopy, there is no contact with

the patient’s eye, which enhances patient’s comfort and reduces the risk of cross-infection. Unlike FFA, no contrast is required, which reduces the risk of adverse drug reaction and anaphylaxis. The newest generations of OCTs allow measurements in patients with undilated pupils as small as 3 millimetres,<sup>16</sup> thus, increasing the convenience of use.

Improved sensitivity

OCT is highly sensitive in detecting early changes such as minimal early macular edema. Hee et al<sup>5</sup> have shown that OCT can detect early retinal changes even when slit-lamp biomicroscopy shows normal findings.<sup>5,8</sup> Brown et al<sup>17</sup> have shown that OCT is better in detecting early retinal edema than biomicroscopy. Serous retinal detachment and vitreomacular interface (VMI) changes can also be more easily visualized with OCT than biomicroscopy.<sup>8</sup>

Correlation with visual acuity

Studies have shown that retinal thickness in diabetic macular edema (DME) correlates well with visual function.<sup>18-24</sup> In the prospective study by Alkuraya et al,<sup>25</sup> central macular thickness was significantly correlated with visual acuity. A study conducted by DRCR.net showed that every 100 micron decrease in central foveolar thickness corresponds with an improvement of visual acuity by 4.4 ETDRS letters.<sup>24</sup> A recent study showed that an increase in central subfield thickness in patients with DME corresponds to worsening of best-corrected visual acuity.<sup>26</sup> Thus, OCT shows advantage over traditional imaging modalities in prediction of visual outcome.

Optical coherence tomography findings in diabetic retinopathy

In the ETDRS, OCT findings were not included because OCT was not commercially available when the study was performed (**Tables 1 and 2**).<sup>1,2</sup> Although OCT assessment

Table 1. Classification of diabetic retinopathy according to the Early Treatment Diabetic Retinopathy Study. <sup>1,2</sup>		
Grade	Findings	Treatment recommended*
Non-proliferative		
Mild NPDR	Presence of at least 1 microaneurysm, but not enough to qualify as moderate NPDR	DM control
Moderate NPDR	Extensive intraretinal hemorrhages and / or microaneurysms, IRMA, venous beading, but not to the degree of severe NPDR	DM control
Severe NPDR	4-2-1 rule: <ul style="list-style-type: none"><li>• Intraretinal hemorrhage and / or microaneurysms in all 4 quadrants;</li><li>• Venous beading in at least 2 quadrants;</li><li>• IRMA in at least 1 quadrant</li></ul>	DM control Consider early prophylactic scattered PRP where progression is likely
Proliferative		
PDR	Presence of NVD or NVE	DM control PRP
High-risk PDR	Any one of: <ul style="list-style-type: none"><li>• NVD ≥1/4 to 1/3 disc area</li><li>• Any NVD with VH</li><li>• NVE ≥1/2 disc area with VH</li></ul>	DM control PRP

Abbreviations: DM = diabetes mellitus; IRMA = intra-retinal microvascular abnormalities; NPDR = non-proliferative diabetic retinopathy; NVD = neovascularization at disc; NVE = neovascularization elsewhere; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; VH = vitreous hemorrhage.  
\* According to the recommendation set out in the Early Treatment Diabetic Retinopathy Study.



**Table 2. Classification of macular edema (i.e. CSME) according to the Early Treatment Diabetic Retinopathy Study.<sup>1,2</sup>**

Definition (at least 1 of following)	Treatment*
1. Retinal thickening $\leq 500$ $\mu\text{m}$ of the FAZ	1. Focal laser to microaneurysms
2. Hard exudates $\leq 500$ $\mu\text{m}$ of the FAZ with associated thickening of the adjacent retina	2. Grid laser to edematous retina within the macular region
3. Retinal thickening $\geq 1$ disc area in size $\leq 1$ disc diameter from the center of fovea	

Abbreviations: CSME = clinically significant macular edema; FAZ = foveal avascular zone.

\* According to the recommendation set out in the Early Treatment Diabetic Retinopathy Study.

**Table 3. Review of optical coherence tomography classification systems by different authors with details.**

Classification	Year	OCT	Grade	Features
Otani et al <sup>18</sup>	1999	TD	N/A	Sponge-like swelling of retina ( $\geq 250$ $\mu\text{m}$ )
				Cystoid macular edema
				Serous retinal detachment
				Hyper-reflective spots (representing intraretinal exudates)
Panozzo et al <sup>27</sup>	2004	TD	Retinal thickness for central zone	
			Normal	$170 \pm 20$ $\mu\text{m}$
			Borderline	190-230 $\mu\text{m}$
			Edema	$\geq 230$ $\mu\text{m}$
			Morphology (E)	
			E1	Simple thickening No clinical visible cystoid spaces
			E2	Cystoid thickening (range from a to c). Defined as circular or ovaloid space with no reflectivity. Cyst has minimal size of horizontal 150 $\mu\text{m}$ and vertical 300 $\mu\text{m}$
			E2a	Mild thickening with 2-4 central small cysts. Cyst size: horizontal 150-220 $\mu\text{m}$ , vertical $\leq 400$ $\mu\text{m}$
			E2b	Intermediate thickening with petaloid cysts or central big cysts. Cyst size: horizontal $\leq 300$ $\mu\text{m}$ , vertical $\leq 600$ $\mu\text{m}$ .
			E2c	Severe thickening with coalescence of cyst with retinoschisis appearance
			E3	Neuroepithelial detachment. Defined as the presence of subretinal fluid above the hyper-reflecting line of the pigmented epithelium. Can be isolated or associated with E1 or E2
			Epiretinal traction (T)	
			Well-defined and continuous hyper-reflective line over inner retinal surface with at least one point of adhesion to retina	
			T0	Absence of epiretinal hyper-reflectivity
			T1	Presence of a continuous line without significant retinal distortion
			T2	Presence of line with multiple points of adhesion with significant retinal distortion
			T3	Anteroposterior traction with 'gull-wings' configuration
Kang et al <sup>28</sup>	2004	TD	Type 1	Thickening of fovea with homogeneous optical reflectivity throughout whole layer of retina
			Type 2	Thickening of fovea with markedly decreased optical reflectivity in outer retina
			Type 3A	Thickening of fovea with subfoveal fluid accumulation and detached retina without foveal traction
			Type 3B	Thickening of fovea with subfoveal fluid accumulation and detached retina with foveal traction
Alkuraya et al <sup>25</sup>	2005	TD	Type 1	Sponge-like retinal swelling
			Type 2	Cystoid macular edema
			Type 3	Serous retinal detachment
			Type 4	Vitreo-foveal traction
Kim et al <sup>29</sup>	2006	TD	DRT	Diffuse retinal thickening
			CME	Cystoid macular edema
			SRD	Serous retinal detachment
			PHT, no TRD	Posterior hyaloidal traction without traction retinal detachment
			PHT + TRD	PHT with TRD
Soliman et al <sup>30</sup>	2007	TD	Pattern 1	Angiogram leak without corresponding change in morphology or thickness of retina
			Pattern 2	Diffuse or localized thickening of ONL/Henle's layer
			Pattern 3	Pattern 2 + cystic changes of ONL/Henle's layer
			Pattern 4	Pattern 3 + cystic changes of INL
			Pattern 5	Pattern 4 + serous detachment of neural retina

Abbreviations: INL = inner nuclear layer; N/A = not applicable; OCT = optical coherence tomography; ONL = outer nuclear layer; PHT = posterior hyaloidal traction; TD = time-domain; TRD = traction retinal detachment.



played a major role in the trial by DRCR.net, a classification of OCT features of diabetic retinopathy/maculopathy was not defined.<sup>3</sup> There are a few proposed OCT-based classification systems but none has been conclusive.<sup>18,25,27-29</sup> This is because most were based on small-scale studies and none has histopathological correlations. Most classifications were based on the OCT changes observed involving: (1) the VMI (above the retina), (2) intraretinal changes (within the retina), and (3) subretinal changes (below the retina). A review of proposed classification systems is given in **Table 3**.<sup>18,25,27-30</sup>

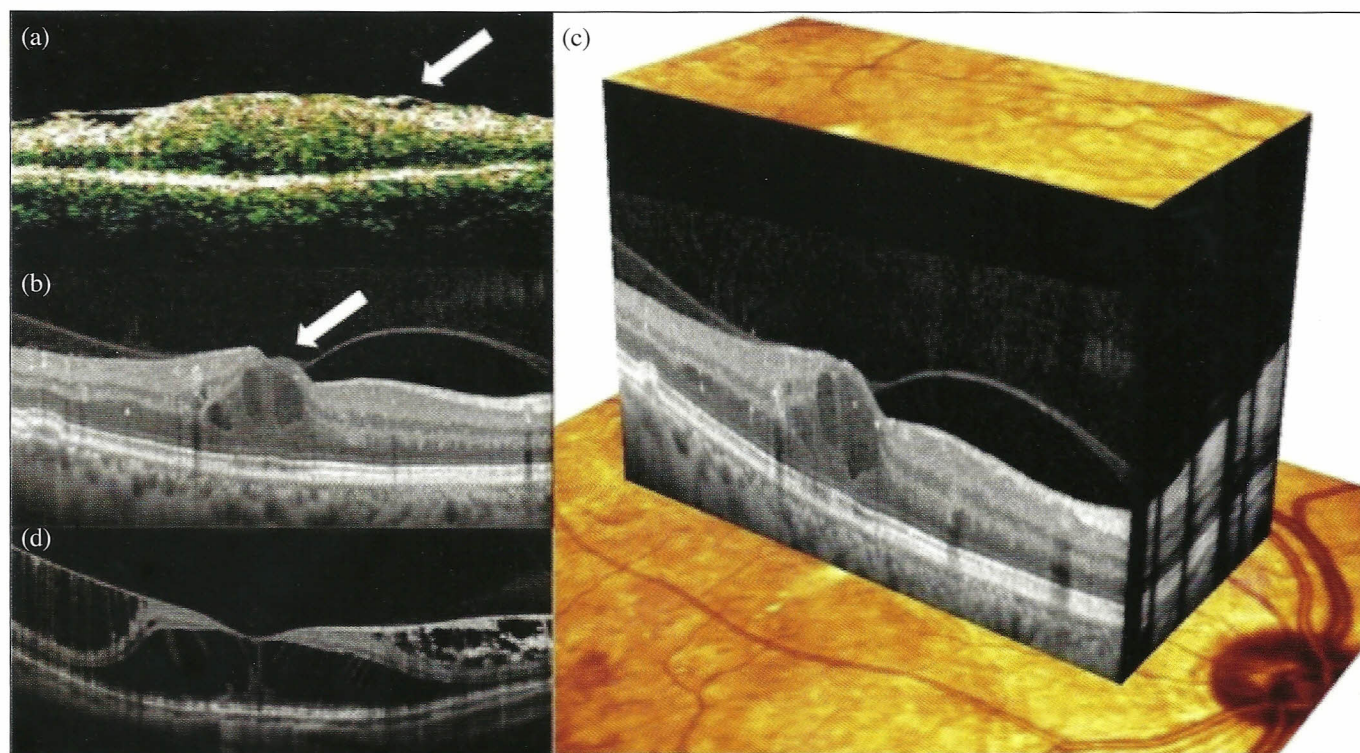
### Vitreomacular interface changes

The vitreous has been thought to play an important role in the pathogenesis of diabetic maculopathy.<sup>31</sup> Vitreomacular traction (VMT) has been proposed to cause macular edema. In recent reports, VMI abnormalities such as posterior hyaloid-retinal adhesion, and epiretinal membrane formation were found to be highly prevalent in eyes with persistent diabetic macular edema (PDME).<sup>19,31-33</sup> Therefore, in macular edema cases with traction, vitrectomy to release a taut adherent posterior hyaloid is the treatment of choice as traditional laser photocoagulation was found to be ineffective. However, the diagnosis of VMT can be difficult without the use of OCT.<sup>31</sup> **Figure 2** shows some VMI abnormalities detected by OCT.

### Intraretinal changes

DME is postulated to be the result of the breakdown of blood-retina barrier. Proteins and exudates extravasated from leaky intraretinal vessels create an osmotic pressure that leads to the formation of retinal edema and cysts. Soliman et al<sup>30</sup> devised a grading system for DME based on OCT findings and correlated with fundus angiogram findings. They found that early DME angiographic leakage could have no morphological change on initial OCT. However, progression of macular edema corresponds with thickening in the outer nuclear layer. Further progression with involvement of the inner nuclear layer is associated with intraretinal cyst formation. **Figures 3a** and **3b** show some intraretinal changes observed with OCT.

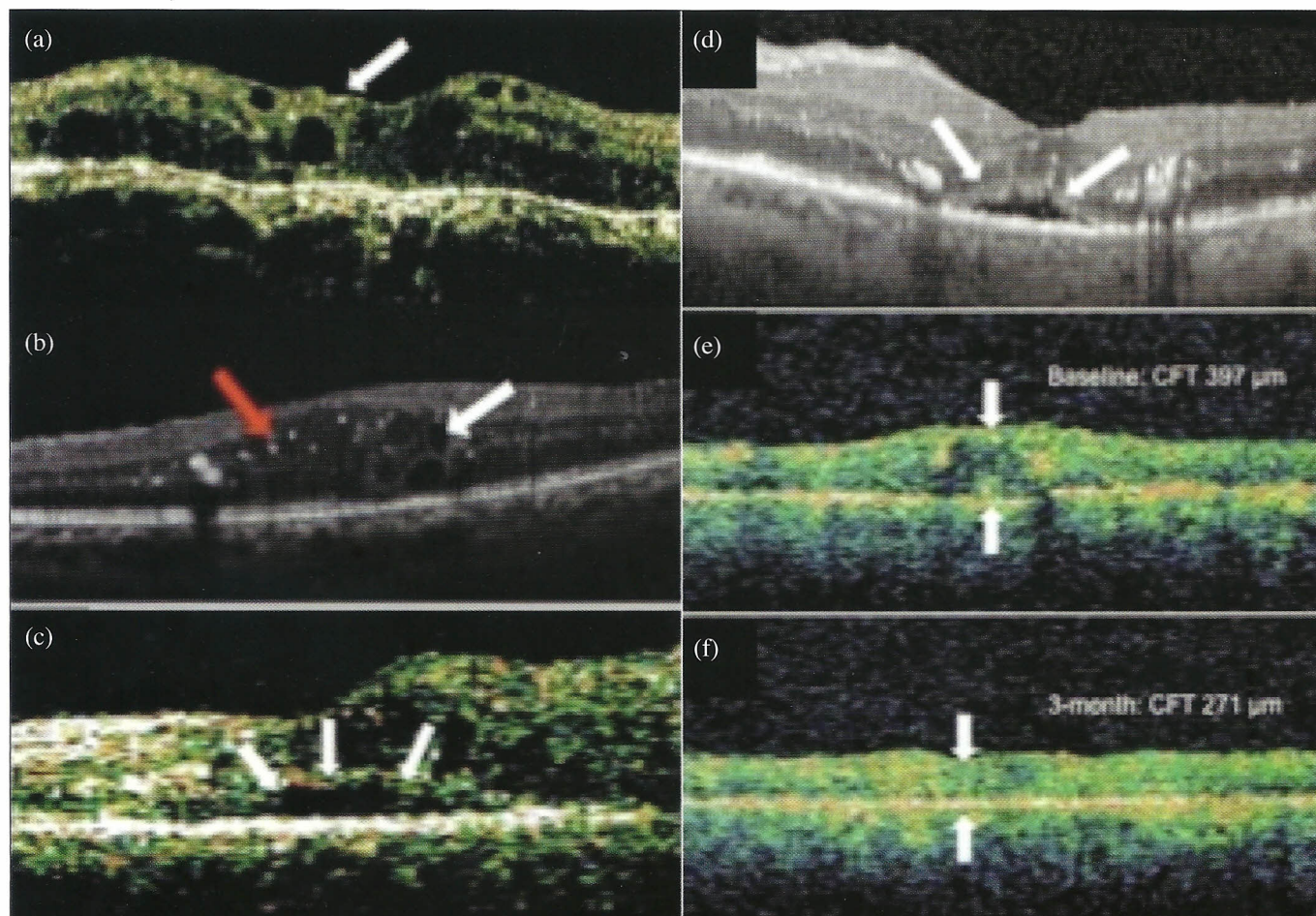
In a recent study using spectral-domain OCT, Bolz et al<sup>34</sup> observed hyper-reflective foci within the retina that could not be visualized previously using time-domain technology. These foci could not be seen on biomicroscopy or fundus angiogram due to their small size (<30 microns) [**Figure 3**]. Bolz et al<sup>34</sup> postulated that these foci might represent extravasated protein due to breakdown of the blood-retina barrier in diabetic retinopathies. Further studies were carried out to delineate the nature of these foci and their correlation with clinical presentation. Although a standardized grading system is yet to be developed, a wide



**Figure 2.** Optical coherence tomography (OCT) images of vitreomacular interface abnormalities.

(a) Time-domain image OCT (Stratus OCT, Carl Zeiss Meditec, USA) showing posterior hyaloid face partially adherent to the fovea (arrow); (b) Spectral-domain OCT (Spectralis OCT, Heidelberg Engineering, USA) showing adherent posterior hyaloids at the fovea causing edema and intraretinal cystic change (arrow); (c) Spectral-domain OCT (Spectralis OCT, Heidelberg Engineering, USA) 3D reconstruction of the same cut in (b); (d) Spectral-domain OCT (Nidek RS-3000 OCT, Japan) showing very advanced vitreoretinal interface abnormality with poor clinical response after traditional laser treatment and requiring surgical intervention.





**Figure 3.** Optical coherence tomography (OCT) images demonstrating intraretinal, subretinal pathologies and before-and-after treatment appearances.

OCT images of intraretinal abnormalities: (a) Time-domain OCT (Stratus OCT, Carl Zeiss Meditec, USA) showing disruption of foveal contour, edema and intraretinal cystic changes (white arrow); (b) Spectral-domain OCT (Nidek RS-3000 OCT, Japan) showing similar intraretinal cyst formation in higher resolution (white arrow); hyper-reflective foci within the retina associated with edema (red arrow), which is not seen in (a).

OCT images of subretinal abnormalities: (c) Time-domain OCT (Stratus OCT, Carl Zeiss Meditec, USA) image showing subretinal serous macular detachment with overlying retinal edema and cystic changes. (d) Spectral-domain OCT (Spectralis OCT, Heidelberg Engineering, USA) image showing similar findings with the addition of hyper-reflective foci within the retina.

Time-domain OCT comparison of pre- and post-treatment macula: Time-domain OCT (Stratus OCT, Carl Zeiss Meditec, USA) image showing the fovea (e) before and (f) 3 months after laser treatment. There is reduction of retinal thickness after successful laser treatment.

variety of morphological changes in diabetic maculopathy are observed with OCT, which allows further understanding of the pathogenesis of DME.

### Subretinal changes

Several reports describe the formation of localized serous retinal detachment in severe cases of diabetic maculopathy.<sup>18,25,27-30</sup> Leaky blood vessels allow extravasation of protein inside the retina; however, extravasation is limited by the external limiting membrane (ELM) due to its smaller pore size. In severe diabetic maculopathy, there is dysfunction of the ELM, allowing large-sized protein molecules to extravasate into the subretinal space, leading to the formation of subclinical serous macular detachment (Figures 3c and 3d).

In recent reports, the incidence of subclinical serous macular detachment ranges from 2.9% to 15% in eyes with severe diabetic maculopathy.<sup>18,25,27-30</sup> In a study looking at serous macular detachment by Kim et al,<sup>35</sup> focal laser photocoagulation showed improvement in terms of macular edema and visual acuity. In a case series by Ozdemir et al,<sup>36</sup> all cases of serous macular detachment regressed after intravitreal injection of 4 mg triamcinolone. However, the effect of intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) on serous macular detachment is not well studied so far. OCT helps to identify this subgroup of patients where 'apparent' macular edema may seem to persist despite repeated treatment. OCT can help in quantitative monitoring of the progress of serous macular detachment before and after treatment.



### Changes in the photoreceptor layer

Some patients with DME do not show improvement in vision despite reduction in retinal thickening after treatment (either in the form of laser or injection of anti-VEGF or steroids). This may be related to the foveal photoreceptor integrity. In particular, the disruption of the inner segment-outer segment (IS/OS) junction has a reported incidence of 49% to 75%.<sup>28-30</sup> Greater visual improvement was observed in those with an intact IS/OS versus those without.<sup>29</sup> In a recent novel index study, disruption of the IS/OS was shown to cause a significant decrease of 3.28 dB in retinal point sensitivity in patients with DME ( $p < 0.001$ ).<sup>37</sup> Other than IS/OS, other hyper-reflective lines in the outer retina have been correlated with visual function in DME.<sup>28</sup> Otani et al<sup>18</sup> reported a positive relationship between the integrity of ELM and vision function. The correlation was even stronger when both ELM and IS/OS were correlated with vision at the same time. This was in agreement with findings from a study conducted by Chung et al<sup>38</sup> in which intravitreal triamcinolone was given for DME. Other than correlation of vision with IS/OS and ELM, Chung et al<sup>38</sup> also found that the length of disrupted layers was a crucial factor. They found that the shorter the length of disruption, the better the visual outcome, or the more likely the restoration of disruption. These studies provide evidence to support the concept that the outer retinal layers could be used as indicators for visual prognosis, as well as predictors of visual outcome following treatment. OCT can, therefore, have a place in the quantitative and qualitative analysis of outer retinal layers.

### Optical coherence tomography-guided treatment

#### As a clinical parameter to guide treatment and re-treatment

In patients with DME, focal laser is currently the standard treatment of choice according to both the ETDRS and DRCR.net (Table 1).<sup>1-3</sup> In the ETDRS guidelines, no OCT parameters were included because OCT was not available at the time. But in recent studies by DRCR.net, OCT was used as a means for primary monitoring in diabetic maculopathy.<sup>3</sup> In one of their studies, re-treatment was guided by OCT measurements of macular thickness, visual acuity and clinical judgment.<sup>3</sup> OCT measurement is now recognized as an important clinical parameter in the clinical management of diabetic maculopathy. Computerized mapping of the macula by OCT can give sectoral macular thickness measurements in specific quadrants. The elevation map is particularly useful for patients to understand the severity of their macular edema and serial measurements can also monitor clinical response to treatment and guide re-treatments (Figures 3e and 3f).

#### Classification by optical coherence tomography patterns to predict outcome

As mentioned, different types of OCT patterns were identified in diabetic maculopathy. Kim et al<sup>35</sup> classified diabetic maculopathy patients into subgroups according to

OCT patterns, and correlated with improvement after focal laser photocoagulation. They have shown that cases with diffuse retinal thickening had greatest improvement in terms of reduction in retinal thickening and increase in visual acuity after focal laser treatment compared with cases with cystoid macular edema, and VMI abnormalities. Therefore, identifying OCT patterns in macular edema allows prediction of outcome after laser treatment.

#### Early detection of high-risk patients

Despite focal laser therapy, macular edema persists in a portion of patients. Different treatment strategies including intravitreal steroid injection, intravitreal anti-VEGF injections and vitrectomy have been advocated in these patients.<sup>39-61</sup> A study by Massin et al<sup>19</sup> found that vitrectomy was more beneficial in eyes with PDME and VMI abnormalities than in eyes with PDME without VMI abnormalities. Now with OCT, we can identify patients with VMI abnormalities and advocate vitrectomy. Furthermore, OCT can help to identify any abnormalities in VMI in proliferative diabetic retinopathy (PDR). In PDR, abnormal retinal new vessels proliferate on the surface of the retina and sometimes into the vitreous. It is often difficult to determine clinically whether the vitreous is still attached to the new vessels. However, there is an increased risk of progression and complications such as vitreous hemorrhage in this group of patients with VMI abnormalities. OCT can play a role in identifying these high-risk patients, so as to allow more aggressive treatment plans.<sup>31</sup>

### Limitations

#### Static imaging

OCT is a static imaging technique; it cannot provide dynamic information like FFA. Dynamic information such as vascular perfusion status is essential in the management of diabetic retinopathy. Evidence of retinal ischemia or vascular leakage alters management. Hence, in clinical practice, FFA and OCT complement each other to guide clinical decisions.

#### Dependence on media clarity

The quality of OCT is highly dependent on media clarity. Projection of infrared light from the OCT can be obscured by any significant opacities along the visual axis. This issue is especially significant in diabetic patients, as they are known to have an increased risk of cataract, vitreous hemorrhage and pre-retinal hemorrhage. All these media opacities may jeopardize the quality of acquired images.

#### Lack of reproducibility and repeatability

Ideally, the same plane of interest should be re-imaged at subsequent follow-ups to allow a fair assessment of the change in retinal thickness.<sup>62</sup> However, eye movements and fixation difficulties may affect reproducibility of the scanned images. To address the concern, the spectral-domain OCTs have been developed to improve reproducibility due to the higher scan acquisition speed. Point-to-point correlation between OCT image and fundus images is now available



for most spectral-domain OCTs. Good reproducibility was reported with a Humphrey 2000 OCT prototype system (Humphrey Instruments, Inc, Dublin [CA], USA), the first commercially available Zeiss 2000 OCT system (Carl Zeiss Meditec Inc., Dublin [CA], USA).<sup>10,11,63</sup> The Cirrus Spectral Domain OCT system was reported to have a high degree of repeatability and reproducibility, which was more than adequate for clinical purposes. Another study using the Humphrey OCT system showed retinal thickness measurements in the macular area to be repeatable and reproducible.<sup>64</sup> These can ensure scanning of the same location at subsequent visits.<sup>65,66</sup>

### Diurnal variation

Several studies have reported issues regarding the time of scanning due to diurnal variations in retinal thickness in diabetic patients; the retina is generally thickest in the morning and is thinner later in the day.<sup>67-71</sup> However, in DME, the difference in central subfield thickening between 8 am to 4 pm is too minimal to account for a change in visual acuity.<sup>68</sup> Hence, the time of scanning is of limited clinical importance.

### Optical coherence tomography in correlation with other modalities

#### Optical coherence tomography in correlation with fundus autofluorescence

Fundus autofluorescence (FAF) is used to assess the capillary nonperfusion state in patients with DME. FAF visualizes the distribution of lipofuscin in the retinal pigment epithelium (RPE) which is mainly produced by incomplete degradation of photoreceptor outer segments, indicative of oxidative damage within the retina.<sup>72</sup> It is reported that lipofuscin accumulates in microglia in higher quantities than in the RPE.<sup>73</sup> Since microglia are activated by diabetes, this activation could determine the oxidation of proteins and lipids that accumulate in the microglia due to ongoing diabetes. A study by Vujosevic et al<sup>74</sup> revealed that macular FAF increases in >75% of patients with clinically significant macular edema and retinal sensitivity decreases over areas with increased FAF. It also showed that patients with increased FAF have poorer macular sensitivity. These findings imply that the sensitivity of the neurosensory retina

and macular function decreases with increase in FAF.<sup>74</sup> Other studies also indicate a strong correlation between OCT findings and FAF patterns in DME.<sup>38,75</sup> FAF, therefore, complements OCT in the prediction of outcome in DME patients.

#### Optical coherence tomography in correlation with microperimetry

Studies have shown that visual acuity in patients with diabetic retinopathy is best predicted and is in direct proportion with macular sensitivity. Macular sensitivity can be determined by microperimetry by assessing central macular function.<sup>76</sup> Microperimetry can also quantify macular sensitivity and correlate with retinal fixation characteristics.<sup>74</sup> Many studies and trials have already reported a significant indirect correlation between macular thickness and its sensitivity.<sup>77-80</sup> Microperimetry can aid OCT in the prediction of visual outcome in patients with DME as it is able to determine macular sensitivity at a specific location of edema. Such functional evaluation of DME is significantly useful as it helps in assessing severity of the disease and to guide treatment outcomes. It can also help in identifying new DME patterns.

### Conclusion

Diabetic eye disease is one of the most important causes of blindness in the world. Early detection, accurate assessment and suitable treatment are vital in the modern management of this disease. Many of the conventional assessment methods are insufficient in detecting early diabetic changes, and lack quantification of the disease. The development of OCT serves to overcome these shortcomings. OCT has been proven to be able to detect early diabetic retinopathy even when slit-lamp biomicroscopy shows normal findings. OCT can quantify DME, facilitate assessment of disease progression before and after different treatments, and predict prognosis including correlation with visual acuity. The use of OCT in diabetic retinopathy and maculopathy supplements clinicians with essential information. It is, therefore, a suggested modality for use in combination with clinical assessment and other imaging modalities for the diagnosis, treatment and monitoring of diabetic eye disease.

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