Introduction

The review of OCT will deal with two prototypical diseases involving the macular vasculature and circulation. Diabetic macular edema is the most common cause of loss of vision in a diabetic. This retinal microangiopathic disease that has protean ways of presentation has lead to a evolution of a tailor made management approach thus deviating from the long honored diktats of the famous trials which first governed DME management. OCT can be considered as being as spark that initiated this evolution and development of OCT seems to parallel the management changes in DME.

AMD especially the exudative variety is a primary choroidal vasculature deviation that later results in changes in the retinal microstructure. AMD management trials exemplify the standardization of protocols incorporating OCT and have governed the pattern of trials to come in near future.

Since its first description in 1991 by Huang and coworkers, time domain OCT has revolutionized the practice of ophthalmology and, in particular, the diagnosis and management of patients with retinal disease

Spectral Domain OCT (SD OCT) has since its use changed the way macular pathology is seen and understood and has created a paradigm shift in the management of vascular diseases. This coupled with advent of newer intravitreal pharmacotherapy has revolutionized retinal therapeutics. The OCT is often required to validate newer treatments and research.

The primary advantage of SDOCT over time domain OCT is its speed. Instead of a moving mirror to assess depth, SDOCT devices use a spectrometer and Fourier mathematics to extract the depth information. In essence, an “A-scan” is acquired “all at once,” thus dramatically increasing the acquisition speed. The current SDOCT devices on the market tout scanning rates of 18,000 – 40,000 A-scans. The high speed of SDOCT has several implications for imaging in patients with diseases such as DME and AMD where the high speed A-scan acquisition allows dense sampling of the macula.

Another major benefit of the high speed of SDOCT devices is improved registration. The rapid and dense acquisition of OCT data facilitates alignment of the B-scans with other fundus images (infrared or color) acquired at the time of the OCT scan acquisition. Another benefit of SDOCT and the dense acquisition of image data is the ability to generate three dimensional renderings of the disease morphology. This is particularly useful in surgical planning for vitreoretinal interface disease. Current limitations are 2–3 μm in experimental systems and about 5 μm in commercial systems. Interpolation between single scans was dramatically reduced and therefore an important source of bias in the volumetric measurements eliminated.

With volumetric datasets available, visualization and processing of three-dimensional (3D) renderings have been investigated extensively. In addition to standard B-scan imaging, C-scans (en face images) and arbitrary oriented sectional images can be derived from the 3D data sets. Segmentation, that is identification and delineation of selected layers, such as the ILM, nerve fibre layer (NFL), inner/outer photoreceptor segment junction and the RPE, is another important feature of SD-OCT technology.

OCT Evaluation

In Diagnosis:

Evaluation using OCT is essentially in two ways. This qualitative evaluation generally includes a screening followed by a detailing methodology. The screening is based on template recognition where there are certain basic tomographic appearances that lead on to a diagnosis. The detailing includes looking for associated more subtle signs that eventually lead on to a modification of the diagnosis.

In Prognosis and Prognostication:

Quantitative evaluation can include many parameters like CFT or central foveal thickness, subfield thickness, maximum macular thickness etc. Registration processes available in new age SD OCT instrumentation allow for pinpoint localization which allows for exact review of area of thickening.

Basic Tomographic appearances in Macular disease

Thickening of Retina:

Uniform thickening of retina occurs in conditions like spongiiform retinal edema. Focal retinal thickening occurs in cystoid macular edema(CME). Thickening of retina may sometimes be associated with contour changes ranging from loss of the fovea depression to gross macular elevation.
Figure 1: Diffuse Retinal Thickeining

Figure represents diffuse retinal thickening associated with Diabetic Macular edema. A - Hard Exudate Clump, B - Spongiform edema, C – Posterior shadowing from hard exudates.

Thinning of Retina:
Thinning of neuro-sensory retina occurs without a generalized change in contour like in foveal atrophy. This may be associated with selective thinning of certain layers like the photoreceptor layer, Outer nuclear layer etc.

Figure 2 – Thinning of retina

This figure represents geographic atrophy in AMD. A – Foveal atrophy, B – RPE scarring.

Retinal Tissue loss:
Tissue loss or reflectivity free spaces appear in conditions like lamellar defects of retina. They may be inner or outer retinal. There may over a widespread area like foveoschisis or may be very localized like the defects in macular telangiectasia, solar burns and lamellar holes.

Figure 3 – Retinal tissue loss

This figure represents lamellar retinal tissue loss. A – Retinal tissue loss, B – ILM draping, C – Photoreceptor layer rarefaction.

Surface changes and vitreomacular interface alterations (VMIA)
Epiretinal membrane may be subtle enough to occur with just surface irregularities of the retina without distortion of the foveal dip or may be severe enough to cause a regular or irregular foveal distortion. This may lend the appearance of a hillock or a peaked mountain respectively.

VMIA generally may cause foveal or para-foveal traction. Often they are associated with sub-macular detachments and CME also.

Figure 4 – Vitreomacular Interface alterations (VMIA)

This figure represents Vitreomacular interface alterations. A – Thickened posterior hyaloid face, B - Vitreomacular traction.

Figure 5 – Surface anomalies

This figure represents Retinal surface anomalies. A – ILM folds, B – Epiretinal membrane, C – Lamellar hole, D – Intraretinal cystoid spaces.

Fluid:
Fluid may be sub retinal, or sub RPE. The ability to pick up subretinal fluid has greatly enhanced the clinician ability to detect activity in AMD and also modify treatment strategies in DME. The presence of sub macular fluid often points to poor systemic control in DME. These are picked up more efficiently with SD OCT than TD OCT.

Figure 6 - Fluid
Reflectivity changes:

Decreased reflectivity changes may be due to media haze. If it is generalized, it may be attributed to cataract. Localized decrease in reflectivity can occur in shadowing due to hard exudates and blood. In these cases, the blood or lipid may appear as a structure with intensely enhanced reflectivity.

Generalized enhancement of reflectivity especially the superficial layers of retina is seen in conditions like CRAO and BRAO where the presence of retinal ischemia contributes to this appearance.

SD OCT in Diabetic Macular Edema (DME)

In diabetic macular edema, vascular endothelial damage is a major event that results in the breakdown of the inner blood-retinal barrier and accumulation of fluid and serum macromolecules in the intracellular space. Instead of qualitative descriptors of disease severity such as “mild,” “moderate,” and “severe,” clinicians were able to characterize the status of their patient’s disease with much greater precision. OCT-derived measurements rapidly became incorporated into clinical trials and clinical practice for monitoring response to therapy, particularly for patients with macular edema secondary to retinal vascular diseases such as diabetes.

This technology has changed our perspective in the management of DME by: (1) accurately diagnosing the different types, especially in the early stages when structural changes may occur that would not yet be evident with slitlamp biomicroscopy or FA; (2) facilitating decisions on treatment protocols (surgical or medical); and (3) aiding as a noninvasive tool in monitoring the disease progress and treatment outcome.

In DME, SD-OCT reveals various pathologic findings on qualitative and quantitative levels, as well as abnormal morphology of retinal layers. The qualitative interpretation includes hyper-reflective (hard exudates and cotton wool spots), hyporeflective (intraretinal edema, exudative retinal detachment, and cystoid macular edema), and shadow effect (hemorrhage, exudates, and retinal vessels).

Some researchers discovered a significant correlation between central foveal thickness and BCVA in diabetic eyes. These findings may be useful for early detection of macular thickening and may be indicators for closer follow-up of patients with diabetes.

Otani et al. were among the first to observe structural changes in DME by OCT, including: sponge-like retinal swelling (88%), edema with cystic spaces (47%), and edema with serous retinal detachment (15%). The same study reported that best-corrected visual acuity was correlated with retinal thickness, regardless of the different tomographic features.

Kim et al. described various tomographic patterns of DME.

They were DRT or diffuse retinal thickening (97%), CME or cystoid macular edema (55%), SRD or subretinal detachment (7%), TRD or tractional retinal detachment (2.9%), and PHT or posterior hyaloid thickening (12.7%). He demonstrated a significant correlation between worse visual acuity and thicker central foveas.

Panozzo et al. further categorized the type of edema and traction. Introduction of vitreomacular traction into the classification of DME had germinated the concept of a surgical management of DM.

Fluorescein angiography (FA) remains a vital tool in the management of DME. Previously a lot of research has gone into validating the use of OCT while comparing it with FA. The idea was to consider a FA less treatment of DME. Though not completely achieving its intended aim many studies have made credible comparisons between the two modalities.

Otani et al. has presented research in this regard. He stated that optical coherence tomography showed that the perifoveal areas with a honeycomb pattern of hyperfluorescence had not only swelling of the OPL but also cystoid spaces located in the inner nuclear layer (INL). The perifoveal areas with no honeycomb pattern but petalloid or diffuse hyperfluorescence had only retinal swelling of
the OPL. In perifoveal areas without hyperfluorescence, OCT showed almost normal retinal structures.

Serous macular detachment and vitreomacular traction in the fovea are seen in OCT but not in FA. The value of SD OCT remains in these areas. In the case of submacular detachments, the lessons learnt were that these patients needed greater attention to their systemic conditions like dyslipidemia, nephropathy and hypertension besides the glycemic control and that often intravitreal agents were required for treatment.

Ozdemir et al.\textsuperscript{17} reported that the incidence of serous macular detachment detected by SD-OCT in diabetic CME was much higher (31%)\textsuperscript{10} than previously reported. In patients with DME accompanied by SRD, SD-OCT revealed that hyperreflective dots may be associated with the subfoveal deposition of hard exudates during follow-up.

Koleva-Georgieva et al.\textsuperscript{18} documented the presence and strength of vitreomacular traction, either by partially detached posterior hyaloid or epiretinal membrane. The partially detached posterior hyaloid appeared as a relatively hyper-reflective line in the nonreflective space of the vitreous body.

Identification of vitreomacular traction is essential for optimal management of DME. Often treatment failure to laser, anti-VEGF and vitreal steroid occurs because of unrecognized traction. Surgical release of VMT may be the only course of management in these eyes.

In ischemic DME, FA is still the best monitoring tool, as OCT will not be able to give much information regarding this particular condition. Newer SD OCT have the capability to demonstrate damage to the IS OS layer which may include rarefaction, focal loss or diffuse loss.

OCT has failed to become a surrogate for evaluation of visual function in DME patients, as central retinal thickness shows just moderate correlation to best corrected visual acuity\textsuperscript{20}.

The integrity of the ELM and IS/OS of the photoreceptors was more strongly correlated with best-corrected visual acuity (BCVA) when compared with central subfield thickness.\textsuperscript{21,22}

**Evaluation of treatment and prognostication using SD OCT**

Laser photocoagulation: Laser is the gold standard for management of DME. While SD OCT has introduced new variables in clinical evaluation, it has also compounded the fallibilities of the ETDRS and DRS studies which failed to address management in the presence of CME, SRD, VMIA and Macular Ischemia.

In a study by Kim et al.\textsuperscript{14} changes in retinal thickness and retinal volume were significantly different for different OCT types after focal laser photocoagulation Change in VA from baseline was not significantly different between groups. The Diffuse Retinal Thickening pattern was associated with a greater reduction in retinal thickening and better VA improvement than the CME or Vitreo macular interface anomalies patterns. Proportions of patients with persistent DME (central macular thickness > 250 μm after laser treatment were greater for the CME and VMIA patterns than DRT pattern.

In itself the effects of laser have been demonstrated to produce alterations of retinal thickness at the location of the laser burns which mainly occurred within the retinal layers that extend from the outer plexiform layer (OPL) to the outer highly reflective layer (HRL).\textsuperscript{21}

Framme et al. have demonstrated postoperative RPE proliferation, RPE atrophy and neurosensory retina alteration seen with SD-OCT following laser.\textsuperscript{24} Thus the future direction of DME treatment will probably be focused more on medical therapy or mild laser, such as selective laser therapy using Nd:YLF, to prevent these structural damages.

**Intravitreal Pharmacotherapy:**

Avitabile et al. reported that intravitreal triamcinolone improved BCVA and reduced central macular thickness more than macular laser grid photocoagulation.\textsuperscript{25} However, the risk of glaucoma has to be considered in patients who are to be treated with triamcinolone.. The Pan-American Collaborative Retina Study group (PACORES)\textsuperscript{26} reported that primary intravitreal bevacizumab for DME seems to provide stability or improvement in BCVA, OCT and FA in diffuse DME at 12 months. Results of the RESOLVE study (Group RS) also showed a promising outcome on safety and efficacy of ranibizumab treatment in patients with DME at 12 months' duration.\textsuperscript{27} A pilot study conducted by Chun et al.\textsuperscript{28} suggested that intravitreal injections of ranibizumab appear to be well-tolerated therapy for patients with DME.\textsuperscript{29} The same study demonstrated that ranibizumab has the potential to maintain or improve BCVA in center-involved DME. An interesting paper by Golbaz et al.\textsuperscript{29} states that in contrast to the sub-RPE compartment, intraretinal and subretinal fluid accumulation demonstrated an immediate response to ranibizumab therapy.

**Surgical Management:**

The identification of obvious surface anomalies like ERMs and VMAs warrant a surgical approach. Improvement of BCVA and significant reduction of macular thickness were documented following vitrectomy for diffuse DME combined with vitreomacular traction.\textsuperscript{30-31} However, the controversy lies in management of recalcitrant edemas without any discernable anomalies. Recchia et al.\textsuperscript{32} suggested that pars plana vitrectomy with ILM peeling may provide anatomical and visual benefit in diffuse DME. In contrast, another
researcher found that vitrectomy and ILM peeling for refractory DME in the absence of vitreomacular traction failed to improve visual acuity.\textsuperscript{33-34}

Despite medical and surgical therapy to reduce the macular edema often there is a failure of improvement of visual acuity. It is suggested that an intact outer retinal complex is vital for visual recovery. Einbock et al. are the first to report the improvement of visual acuity after intravitreal anti-VEGF therapy in patients with normal appearance of the external limiting membrane, photoreceptor inner segment and outer segment, and the RPE.\textsuperscript{35} In contrast, patients with disturbed outer retinal layers on SD-OCT showed only reduction in retinal thickness, without much visual improvement after intravitreal anti-VEGF therapy. Another important finding is that patients with discontinuity of the inner retinal layer and disturbed outer retinal layers failed to achieve anatomical or visual improvement after intravitreal anti-VEGF in DME.

OCT thus bring into significance two situations in DME that were previously nit addressed. They are sub macular detachments and vitreo macular interface anomalies. Greater success in managing these condition has lead to overall improvement in outcomes.

**OCT in Age Related Macular Degeneration**

The nidus of activity of disease in AMD lies in the Outer Retina. On OCT the outer retina is reportedly considered as 4 bands. The substrate of the first hyperreflective band is the external limiting membrane (ELM). The second band appears to reflect the interface of the inner and outer segments of the photoreceptor layer (IPRL), the third band is assumed to represent the outer segment-RPE interdigitation (OS/RPE), and the fourth band may reflect the RPE/Bruch’s membrane complex.\textsuperscript{36,37}

![Figure 9 – Hyper reflective bands in the outer retina](image)

**Changes in Dry AMD**

**Drusen & Drusenoid PEDs:**

Khanifar et al\textsuperscript{38} al has described various tomographic details of changes seen in drusen and drusenoid PEDs. They were defined according to the following characteristicss:

- The shape was defined as 1. Concave (Pointed) 2. Convex (Dome shaped) or 3. Saw tooth or jagged appearance of RPE. The internal reflectivity of the drusen was described as being low, medium or high. The homogeneity of the content was considered as either homogenous or no homogenous. The presence of Hyper-reflective points within the retina above PED was noted. There is reduced thickness of Photoreceptor layer over drusen.

![Figure 10 – Drusen and Drusenoid PED's](image)

This figure represents changes of dry ARMD. A – RPE bumps, B – Drusenoid PED, C – Confluent soft drusen

**Soft Drusen:**

Soft drusen present as dome-shaped elevations of the RPE band in OCT. More elongated elevations can be observed that may be consistent with sub-RPE deposits (e.g., basement membrane deposits)\textsuperscript{39}. Attenuation or disappearance of the IPRL in the OCT scans seems to be in accordance with morphologic alterations of the photoreceptors in the perilesional zone.

Above soft drusen, alterations of the RPE, IPRL (band 2), ELM (band 1) and ONL, respectively, can be observed by OCT imaging; this observation is in accordance with the histologic findings in drusen-related atrophy, where the degeneration of the RPE preferentially occurs over drusen and photoreceptors and the ONL subsequently disappear.

**Geographic Atrophy:**

The changes in an area of GA include

- Thickening of band 4
- Elongated elevation of band 4 with plaques beneath
- Dome-shaped elevations with preserved layers above
- Dome-shaped elevation with clumps at the top
- Dome-shaped elevation with backscattering material beneath
- Spike with a clump at the tip
- Clumps at different retinal levels
- Clump in the OPL with disrupted bands beneath
- Small elevations of band 2 and mottled band 4
- Increased distance between band 2 and band 4.

Thinning and thickening of band 4 was a common finding.
Figure 11 - Geographic atrophy

This figure represents changes seen in geographic atrophy. A – Foveal atrophy, B – Disciform RPE scar, C – Posterior hyaloid face.

In the perilesional zone, distinct morphologic alterations included elevations of the outer retinal layers, thickening, and spikes of the outer hyperreflective band as well as clumps at different neurosensory retinal levels. At the junction, highly variable transitions of the outer retinal layers were present with different degrees of loss of the normal hyperreflective bands. Within the actual GA, hyperreflective clumps at different retinal levels, segmented plaques of the outer band and elevations with variable reflectivity were visualized.

Thinning or thickening of the RPE band in the OCT scan may indeed reflect boundaries of enlarged or attenuated RPE cells. Hyperreflective clumps at different retinal layers can be visualized that correlate with funduscopically visible hyperpigmentary changes; these findings are in accordance with recently reported RPE changes imaged by ultrahigh resolution OCT in eyes with nonexudative AMD by Pieroni et al.

OCT in Wet AMD

The application of OCT in Wet AMD should be to ascertain information so as
- To delineate the extent of lesion
- To evaluate the type of lesion
- To visualize and categorize PED
- To monitor CNV activity and response to treatment
- To evaluate the role of abnormal vitreomacular adhesion in AMD

Various studies prove that SD OCT is superior to TD OCT in discovering activity in eyes with AMD. Three dimensional scans allow visualization of the entire scanned area, resulting in a superior ability to detect CNV activity over linear scans and the TD-OCT’s radial line/fast macular thickness map scans. Spaide et al demonstrated enhanced imaging of the deeper layer of the retina by creating inverted images with the SD OCT.

Evaluation of CNVMs

A CNVM is comprised of a dynamic proliferation of fibrovascular tissue through Bruch’s membrane. Gass et al. used enucleated eyes and classified the neovascular growth pattern as sub-retinal pigment epithelial (RPE) (type 1), subretinal (type 2), or combined.

Signs of CNVMs on OCT:

A classic CNVM shows a thickening or disruption of the RPE-choriocapillaris complex and thickening of retina and subretinal fluid.

Occult CNVM shows a disruption of the RPE-choriocapillaris complex and most of the fibrovascular complex lies under the RPE.

There may be associated subretinal fluid and retinal edema.
A fibrovascular PED is seen as an elevation of RPE with some amount of reflectivity under it.

A hemorrhagic PED is seen as an elevation of RPE with shadowing of the choroidal layers.

Correlation between SD OCT and FA:
The location of the area of leakage in the angiography image often corresponds well to the location of the hyper-reflective subfoveal mass in OCT B-scans, suggesting the penetration of a neovascular membrane through the RPE Bruch’s complex. Although in a clinical setting, a CNV is identified, localized and classified based on its appearance in FA, the accuracy in determining the location of the lesion is uncertain. Recent reports suggest that angiography alone might not be sufficient to determine the exact location. Alam et al raised the question of whether FA is adequate for determining the full extent of the CNV complex. FA might only show active parts of the CNV, whereas FD-OCT might be able to visualize the full extent of accompanied morphological changes. In end-stage AMD with fibrovascular scar development, FD-OCT showed the extent of fibrotic tissue and revealed additional complications such as a neurosensory retinal detachment with fluid accumulation due to retinal traction.

Vitreo-macular traction in AMD:
Hyaloid adhesion to the macula is associated with AMD, and frequently causes VMT in eyes with CNV. Tractional forces may antagonize the effect of anti-VEGF treatment, and cause pharmacological resistance in a subpopulation of patients.

Treatment and Research protocols based on OCT:
Many trials recommended OCT to guide treatment decisions with Ranibizumab in CNV resulting from AMD, instead of monthly injections. Examples of such trials are the PRONTO.
OCT thus provides a platform on which current treatment protocols are validated, newer drugs and treatment are tested and the patient’s condition can be continuously monitored in an objective fashion. It is therefore safe to say that in combination with anti VEGF agents, SD OCT is definitely the greatest single most innovation in retinal management.

References:
22. Otani et al. (Retina 2010; 30(5):774-80)


38. Khanifar AA, Koreishi AF, Izzat JA, Toth CA. Categorization of the various ultrastructural patterns of drusen, visible with high-resolution SD-OCT imaging, to correlate these tomographic features with severity of disease and risk of progression in AMD. Ophthalmology 2008;115:1883–189.


