Review Article

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Assessment of Inner and Outer Retinal Layer Changes in Diabetic Retinopathy

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Abstract

Spectral domain-Optical coherence tomography (SD-OCT) provides information about the in-vivo histology of the retina. Diabetic retinopathy is associated with structural changes within the retina. Recently, disorganization of the inner retinal layers has also been shown to correlate with the final visual outcome.These changes can be observed by OCT, and correlate with the visual acuity. Accurate evaluation of the second hyper reflective band in the macular region, Ellipsoid Zone, on OCT is highly significant for providing valuable information regarding disease state and visual prognosis in diabetic retinopathy.We report on the most current and accepted information regarding this disorganization of inner retinal layers and outer retinal layers and its accurate clinical evaluation

Keywords: Retina; Retinal Layer; Diabetic Retinopathy.

Introduction

Diabetic retinopathy is one of the leading causes of vision loss worldwide [1]. Optical coherence tomography (OCT) provides information about the *in-vivo* histology of the retina. Diabetic retinopathy (DR) results in structural changes within the retina that can be observed by OCT imaging. These structural changes correlate with the severity of vision loss [2]. On spectral domain optical coherence tomography (SD-OCT), a good correlation has been observed between macular thickness parameters and visual acuity (VA) [3,4].

A significant association between disorganization of microstructural architecture of retina and impairment of VA has been observed in Diabetic Macular Edema (DME). Disorganization of retinal inner layers (DRIL) and disruption of outer retinal layers (ORL) contribute to significant decrease in VA in DME (Table 1).

Table 1

DRIL	ORL
Ganglion cell layer (GCL)	External limiting membrane (ELM)
Inner plexiform layer (IPL)	Ellipsoid zone (EZ)
Inner nuclear layer (INL)	Cone outer segment tips (COST)
Outer plexiform layer (OPL)	Retinal pigment epithelium (RPE)

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Disorganization of Retinal Inner Layers

DRIL has emerged as an important parameter on SD-OCT in DME evaluation. It is defined as the horizontal extent for which any boundaries between the four inner retinal layers are not identified. These layers include: ganglion cell–inner plexiform

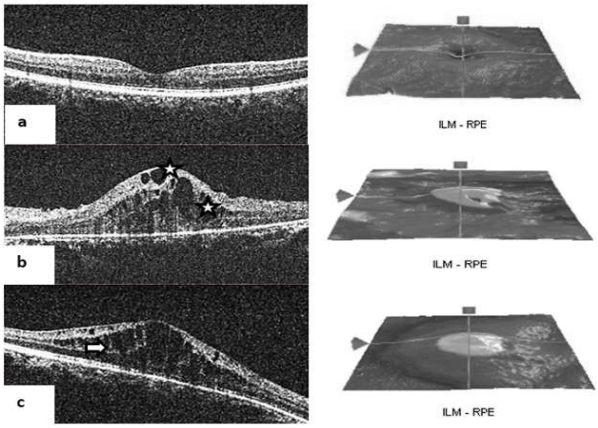

Fig. 1: (a) SD-OCT cross-sectional image shows normal OCT and ILM-RPE overlay map shows normal macular thickness.
(b) SD-OCT cross-sectional image shows cystic spaces in inner retina (*star*) and ILM-RPE overlay map shows increased macular thickness.
(c) SD-OCT cross-sectional image shows extensive cystic changes in inner retina (*arrow*) and ILM-RPE overlay map shows increased macular thickness.

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layer complex (GCL+ IPL), inner nuclear layer (INL) and outer plexiform layer (OPL) (Figure 1). It has been established as a non-invasive predictor of VA in eyes with center-involving and center-sparing DME.

Various studies have been conducted in order to evaluate the association of changes in DRIL with VA. On SD-OCT, the 1-mm-wide retinal area centered on the fovea was evaluated by masked graders for DRIL extent, cysts, hyperreflective foci, microaneurysms, cone outer segment tip visibility and external limiting membrane or photoreceptor disorganization and reflectivity. The study concluded thatan early change in DRIL was associated with a substantial decrease in VA. [5]

The correlation of DRIL with VA after the resolution of macular edema in diabetics was further established. Central 1500-µm macular region was analyzedfor changes, including cysts, DRIL length and extent, and outer retinal layers disorganization. VA after DME resolution correlated with baseline VA. It was found that the patients whose DRIL resolved, both early and late, showed improvement in their VA compared with non-resolvers, whose VA worsened. The study concluded that the presence of DRIL at baseline and its resolution pattern may be associated with subsequent VA improvement after resolution of center-involved DME [6].

The mean ganglion cell layer and mean retinal nerve fiber layer are also observed to be thinner in patients with DR as compared to patients with no DR. Thus, a significant thinning of different inner cell layers and the central retina is present in patients with early DR compared to normal eyes [7].

Outer Retinal Layers

Outer retina has four discrete bands. External limiting membrane (ELM) is the innermost layer present as a linear confluence of junctional complexes between Muller cells and photoreceptors. The ellipsoid zone (EZ) is the second hyper reflective layer.The third layer is the interdigitationzone (IZ) between cone outer segment tips and apical processes of Retinal Pigment Epithelium (RPE). The highly-reflective outermost band represents the RPE/ Bruch's complex [8,9]

In the year 2011, Spaide and Curcio highlighted that the second band initially ascribed as inner segment-outer segment junction (IS-OS) of photoreceptor was principally the EZ of the photoreceptor [10]. With the cellular level resolution obtained by OCT, multivariate analysis demonstrated statistically significant relationship between VA and percentage disorganization of EZ. Furthermore, macular volume change was also found to be significantly associated with visual acuity [11].

An association has been found between the status of the ELM prior to treatment and visual outcomes post treatment in pathologies like epiretinal membranes, age-related macular degeneration and DME. [12-14] ELM is considered as third blood barrier and is formed by zonulae adherens and tight junctions. The shortening of the photo receptor inner segment might be asecondary consequence of the fragmented ELM, therefore disorganization of the ELM is noted earlier than EZ disorganization.Our earlier research has highlighted the importance of an intact ELM at the fovea for retinal photoreceptor microstructures integrity and visual acuity.

Our previous studies have also highlighted a positive correlation between the increase in serum vascular endothelial growth factor (VEGF) and Intercellular adhesion molecule-1 (ICAM-1) levels with severity of diabetic retinopathy. A positive correlation was observed between the grades of ELM and EZ disruption and the levels of VEGF and ICAM-1. Also, the grades of ELM and EZ disruption significantly correlate with decrease in VA [15].

Recently, a significant correlationbetween the macular thickness parameters, disorganization of EZ and the increase in severity of diabetic retinopathy has also been documented (Figure 2). It was observed that severity of DR was associated with increase in disorganization of EZ. 'Global' disorganization of EZ was more prominent in proliferative diabetic retinopathy as compared to non-proliferative diabetic retinopathy. The decrease in VA was observed to be significantly associated

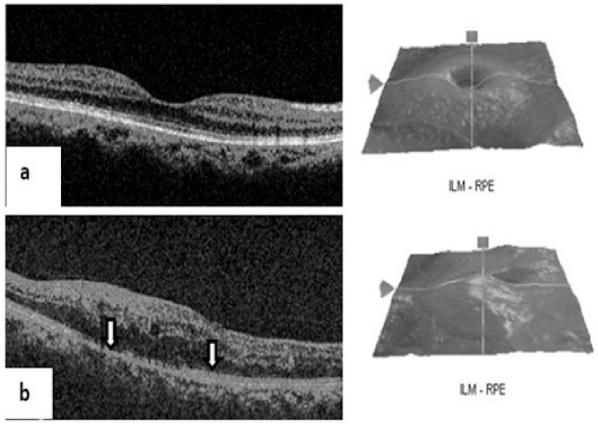

Fig. 2: (a) SD-OCT cross-sectional image shows normal outer retinal layers in OCT and ILM-RPE overlay map shows normal macular thickness.
(b) SD-OCT cross-sectional image shows disrupted ellipsoid zone in the outer retina (arrow) and ILM-RPE overlay map shows increased macular thickness.

with increased disorganization of EZ and severity of retinopathy [16].

Factors affecting integrity of Ellipsoid zone:

The advanced glycation end products lead to an increase in ICAM-1 and VEGF levels. ICAM-1 further causes an increase in the leucocyte adhesion to retinal endothelial cells, which results in retinal micro vascular injury. Increased VEGF levels lead to the breakdown of blood retinal barrier. Increase in the levels of N-CML, ICAM-1 and VEGF results in EZ and ELM disorganization [17]. Increased levels of plasma lipooxygenase, nitric oxide (NO) and decreased levels of reduced glutathione GSH are also associated with in-vivo structural changes in EZ [18].

Retinal pigment epithelium:

Retinal pigmented epithelium (RPE) is a constituent of the outer blood retina barrier and is considered important for the maintenance of the integrity of retina. An increase in the plasma levels of Lipid peroxide, NO and decrease in the plasma levels of GSH, EZ disorganization and RPE topographic alteration showed a significant association with increased severity of diabetic retinopathy [17]. Single layer retinal pigment epithelial map has been used to evaluate the topographic alterations in RPE [18].

Factors affecting topography of RPE:

Increase nitric oxide levels are responsible for RPE damage and thus, cause breakdown of the blood retinal barrier in diabetics. RPE is responsible for transport of ions, retinal proteins, growth factors and metabolism of the photoreceptor layer. NO leads to decreased rod outer segment phagocytosis by RPE cells.

Exogenous NO also leads to an inhibition of RPE cell proliferation. Neuronal retina and photoreceptors are the most affected intraocular tissues when RPE is damaged. Increased levels of NO and LPO were found to be a significantly association with VA and topographic alterations in RPE [18].

Classification Systems For Outer Retinal Layer Disruption

Various classification systems have been devised in DR to prognosticate visual acuity.

1. Maheshwary et al graded disorganization from grade 0-2. [15]

i) Grade 0: intact EZ

ii) Grade 1: focal EZ disorganization of 200 microns or less.

iii) Grade 2: EZ disorganization more than 200 microns.

Grades from each patient's horizontal and vertical scan were added to yield a global disorganization scale. Percentage disorganization of photoreceptors EZ was an important predictor of visual acuity among DME patients.

2. Classification system for ELM and EZ Disorganization was given by Jain et al [13]

i) Grade 0: no disorganization

ii) Grade 1: elm disrupted EZ junction intact.

iii) Grade 2: both ELM and EZ junction disrupted

3. In the study by Sharma et al., a simplified, comprehensive and physician-friendly approach of grading EZ disorganization was developed [16]. EZ is graded on horizontal and vertical scans as 'focal' and 'global'.

i) Grade 0: Intact EZ.

ii) Grade 1: Focal disorganization (localized, subfoveal EZ disorganization)

iii) Grade 2: global disorganization (generalized EZ disorganization throughout the macular cube).

4. Study by Sharma et al proposed another classification system for RPE alterations in diabetic retinopathy [16].

i) Grade 0: No RPE alterations

ii) Grade 1: RPE alterations in up to two quadrants

iii) Grade 2: RPE alterations in more than two quadrants.

Conclusion

DRIL and ORL are important predictors of VA in patients with Diabetic retinopathy. The integrity of outer and inner layers on OCT correlates well with final visual acuity and response to treatment in DME.

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Conflicts of Interest – None

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