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Review

Ellipsoid Zone on Optical Coherence Tomography: a review

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ABSTRACT

Emergence of the high-resolution optical coherence tomography has allowed better delineation of retinal layers and many of the anatomical correlations of these layers have now been agreed upon. However some anatomical correlates still remain contentious, such as the second hyper-reflective band which is now termed ellipsoid zone. Despite the lack of consensus of the actual origin of the ellipsoid zone, there has been much interest in evaluating its integrity and intensity in different disease processes. This review paper aims to provide an overview of the ellipsoid zone and its clinical and research applications.

Keywords: Retinal-imaging, Retinal disease, Diagnostic studies, Diagnostic techniques

INTRODUCTION

Since its first emergence two decades ago, optical coherence tomography (OCT) has revolutionized our ability to visualize the retina *in vivo* and to identify the anatomical correlates of pathological changes in ocular diseases. As such, it has facilitated in the clinical management of various retinal and optic nerve conditions.[1]

OCT has demonstrated its potential for identifying novel markers of different disease states as it allows detection of ultrastructural changes in the retina when there is no clinical correlate to visualize. Improved resolution with advances in OCT technology has allowed the delineation of individual retinal layers providing more information to increasing our knowledge of specific subclinical changes in many retinal diseases such as drusen ultrastructure in age-related macular degeneration (AMD),[2] optic nerve head and retinal nerve fibre layer in glaucoma.[3-5] The emergence of the spectral domain OCT (SD-OCT), has allowed better delineation of retinal layers such as the vitreoretinal interface, inner and outer retina, retinal pigment epithelium (RPE) and choroid. Many of these layers have been universally agreed upon, however some anatomical correlates remain contentious,[6] such as the second hyper-reflective band. This band was previously believed to represent the junction between the inner and outer segments of the photoreceptors.[1, 7, 8] More recent evidence suggests that the second hyper-reflective band corresponds with the anatomical location of the ellipsoid portion of the photoreceptors inner segment.[1, 7, 8] In an effort to come to a consensus on the anatomical correlates with OCT description of each layer, an international panel with expertise in vitreoretinal diseases and imaging met in 2014 to access available evidence and provide recommended OCT terminology.[6] The international nomenclature consensus panel recommended the second hyper-reflective band be termed as the ellipsoid zone (EZ), as it avoids attribution of the OCT feature specifically to a single anatomic structure until more definitive evidence becomes available and this paper will use this terminology throughout. Despite the lack of consensus of the actual origin of the EZ, there has been much interest in its appearance particularly evaluating its integrity and intensity in different disease processes.[9-24] In this review paper, we provided an overview of the EZ and its clinical and research applications.

Optical Coherence Tomography

OCT is a non-invasive imaging modality that produces high-resolution cross-section images of the retinal microanatomy.[25] The principle of OCT is based on low coherence interferometry, which analyses the difference in back-scattered light from tissues.[25, 26] OCT utilises a broadband light source, which is first split into a reference and sample beam. With the back-scattered beam from the retina generating an interference pattern with the reference beam, a reflectivity versus depth profile can be constructed.[25, 27] Initially, OCT was only able to provide axial resolution of around 10 to 20 microns, which did not allow for the further differentiation of the neurosensory retina and the RPE, which appeared as one single highly reflective band.[28] Earlier generation time-domain OCT (TD-OCT) like Stratus OCT (Carl Zeiss Meditec, Inc, Dublin, CA) employed time-domain method that allowed a 400 A-scans per second scan rate with an axial resolution of 8 to 10 microns.[27] The newer generation spectral-domain OCT (SD-OCT), such as the Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany) and Cirrus OCT (Carl Zeiss Meditec, Dublin, CA, USA), employs an interferometer and spectrometer which analyses back-scattered light interference pattern simultaneously through Fourier Transform algorithm.[29, 30] This innovative technique enabled an axial resolution of 5 to 7 microns, faster scan rates at 20000 to 52000 A-scans per second and better signal-to-noise ratio compared to TD-OCT.[26, 29-32] The improved delineation of different retinal layers makes this modality ideal for clinical diagnosis and management of ocular diseases (Figure 1).

Retinal Ultrastructures Visualized by OCT

Based upon early TD-OCT, structural correlations with the OCT images were first reported. In 1991 a TD-OCT was capable of producing a single A-scan in 1.25 seconds with an axial resolution of 17 microns.[25] The inner retina hyper-reflective zone was reported to represent the nerve fibre layer, but the outer retina hypo-reflective zone was not further described. Using different animal models, comparisons between OCT images and histological data were considered. Using Macaca mulatta, Toth et al. found that the outer nuclear layer (ONL) and the inner and outer segments of the photoreceptors had low relative reflectivity.[33] In a study using chickens, Huang et al showed a hyper-reflective zone in outer retina, which they speculated to be associated with the increase in local refractive index at the photoreceptor inner segment due to the presence of mitochondria.[34]

In early 2000, the ability to perform higher resolution OCT allowed various layers of the outer retina to be delineated. Three to four distinct hyper-reflective bands on SD-OCT can be identified in the human outer retina.[35] The first band is the innermost and the least intense of the four hyper-reflective bands, which is thought to originate from the external limiting membrane (ELM).[36] The second band is now referred to as the EZ.[6] The histological correlation of the third band is still debated as it has been attributed to the cone outer segment tips,[37] Verhoeff's membrane,[35, 38] or as the intermediate line but is referred to as the interdigitation zone.[39] The fourth band is thought to represent the RPE with contribution from both Bruch's membrane and the choriocapillaris.[40]

Origin and Significance of the Ellipsoid Zone

The second hyper-reflective band has been traditionally ascribed to the IS/OS junction of the photoreceptors.[41] However, recent studies suggest that this band is anatomically correlated with the photoreceptor inner segment ellipsoid (ISe),[1, 7] and is referred to in the international nomenclature consensus as the EZ.[6] The photoreceptor ISe has a high refractive index, leading to increased back-scattering of light that translates to the bright appearance of the EZ.[42-45] The photoreceptor ISe is densely packed with mitochondria and is thus important for the photoreceptor health and function. Hence, the ability to link a signal from this band with a diseased state would be interesting and suggestive of mechanisms at play in disease causation.

Using adaptive-optics, Jonnal et al argued that the EZ is both too thick and proximally located to be generated by the ellipsoids of the inner segments.[46] However, only the foveal cone was imaged in that study which may explain the inconsistent findings with the earlier reports. Although the exact anatomical correlation of the EZ remains disputed, its roles in the clinic and in research is still relevant since change in its integrity and intensity has been correlated with different retinal disease processes.[9, 21, 40, 47-49]

Changes in the Ellipsoid Zone in Different Disease Processes

Changes in the EZ are determined based upon its integrity or intensity. The integrity of the EZ can be characterised broadly into 3 categories of presence, disruption or absence. More recently, a quantitative approach of determining the relative intensity of the EZ has been advocated. The relative intensity of the OCT EZ can be expressed as a ratios of the EZ to the ELM.[10-12] The intensity of the ELM layer is used as the reference value to control for the variation in the brightness of different OCT scans because the ELM is a non-neural layer, does not alter its intensity with age or the stage of degeneration and as it has a consistent intensity across the retina.[10] The INL layer has also been investigated for the use as a reference layer because it has a larger area compared to the ELM, which could have made the manual measurements of the intensity easier. At present the ability to determine the intensity of the EZ nor the ratio with the ELM is not automated so that time consuming manual examination is required.[10-12, 17] The EZ integrity and intensity have been studied in various retinal conditions.

Retinal and macular degenerative conditions

Changes in EZ intensity have been reported in retinal degenerative conditions. Hood et al investigated the intensity of the EZ in cone dystrophy, a condition known to have reduced number of functioning cones, and found that the disease produced a less intense signal from the EZ compared to healthy controls.[17] Sundaram et al investigated the EZ intensity in patients with achromatopsia and its implication in establishing measures to determine patients suitable for gene therapy.[12] They found that those without any disruption in the EZ, the mean intensity ratio of the EZ was significantly lower in achromatopsia compared to controls, but there was no correlation between intensity and retinal sensitivity measured by microperimetry.[12] Furthermore, a case report of peripheral cone dystrophy has found that the reduction in the OCT EZ intensity to be correlated with the reduction in cone photoreceptors in the corresponding area imagined by adaptive optics.[50]

In our own studies we found that patients with the early stages of age-related macular degeneration (AMD) exhibit reduced relative intensity of the EZ when compared to healthy controls across different retinal eccentricities, except at the fovea.[11] We have also observed a correlation between the reduction in relative intensity of the EZ with delayed multifocal electroretinogram (mfERG) implicit time, but not with the mfERG amplitude.[10] In a separate study in eyes with intermediate AMD, we observed the recovery of the EZ integrity following drusen regression without evidence of nascent geographic atrophy. The recovery of the EZ integrity was associated with the improvement in retinal function as measured by the mfERG (Figure 2).

Interestingly the age-related maculopathy susceptibility 2 (*ARMS2*) gene, implicated in AMD, is considered by some to have a role in mitochondrial homeostasis, impacting upon the cellular apoptosis pathway of the cones, although there is not universal agreement on the role of this gene.[51] A decrease in the EZ intensity may be reflecting the reduction in healthy or functional mitochondria in the photoreceptor inner segment, which could translate to abnormal photoreceptor function. Therefore, a quick retinal scan with OCT could potentially detect AMD patients with *ARMS2* genotypes and provide a surrogate measure of retinal function.

Disruption of EZ has also been reported in AMD eyes with reticular pseudodrusen (RPD)[14, 20, 52] and it has been shown to be associated with the reduction of cone density.[14] In a longitudinal study in eyes with RPD, Spaide et al found that eyes progressed to atrophy were associated with loss of photoreceptor length, disruption of EZ band or decrease EZ intensity, and visual loss.[53] In eyes with geographic atrophy secondary to AMD, it has been demonstrated that retinal areas with disrupted EZ have a greater risk for progressing to dense scotoma compared with areas with intact EZ.[54] Several retrospective studies have investigated the EZ changes in patients treated for neovascular AMD,[55, 56] with the presence of the EZ associated with better final visual acuity following photodynamic therapy than in those where the zone was missing.[57]

Inflammatory diseases

Disruption of the EZ has been observed (Figure 3) in patients with multiple evanescent white dot syndrome (MEWDS).[9, 58, 59] Hashimoto et al described diffuse disruption of the EZ in the acute stage, with restoration of the EZ in the intermediate stage and its complete restoration in the late stage of MEWDS.[59] The disappearance of the EZ is initially thought to be related to the structural change in the photoreceptor secondary to disease process, which alters its refractive property and makes it invisible on OCT. However it is noted that the band reappears as the disease evolves suggesting perhaps that the disruption is likely a reflection of altered refractive characteristics which resolve as the inflammation resolves, rather than a permanent loss of cells or their function.[9]

Other inflammatory conditions associated with changes in EZ integrity include acute posterior multifocal placoid pigment epitheliopathy (APMPPE), punctate inner choroidopathy (PIC) and AZOOR. In APMPPE, the EZ is often disrupted in the acute stage of the disease [60] but EZ disruption can also be seen after healing in areas that initially appeared normal on OCT.[61] EZ disruption is also observed in PIC[62 63] and it is usually associated with the focal elevation of the RPE.[64] In AZOOR, the EZ is often irregular or disrupted at the lesion sites or retinal areas with abnormal mfERG.[65, 66] Recovery of the EZ integrity has also been reported in some AZOOR patients when retinal function and enlarged blind spot improved.[67]

Other retinal conditions

The integrity of the EZ has been found to be an important indicator of visual outcomes,[68] and its normal appearance is associated with better post-operative visual acuity in idiopathic macular hole,[22, 69] epiretinal membrane,[70-72] and in retinal detachment.[73-75] Other retinal diseases, where the integrity of the EZ was found to correlate with visual outcome include macular telangiectasia,[76] retinal vein occlusion[77, 78] and central serous chorioretinopathy.[79, 80]

The association between the EZ integrity and visual outcome has also been demonstrated in diabetic macular oedema. The extent of the EZ disruption was found to be a predictor of visual outcome in diabetic macular oedema.[81, 82] It has been shown in a retrospective interventional study that the shorter length of disruption in the EZ correlated with better visual outcome in patients with diabetic macular oedema treated with intravitreal triamcinolone.[83] In a study of diabetic retinopathy where there is angiographic evidence of macular non-perfusion, the authors have reported corresponding SD-OCT demonstrating both disruption of integrity and reduced intensity of the EZ.[84]

Changes in EZ integrity have also been demonstrated in ocular infectious conditions such as syphilis[85] and dengue fever-associated maculopathy.[86]

En-face OCT Imaging Techniques

En-face OCT imaging was first reported in literature in 1997.[87] Wanek et al have identified the EZ en-face images and demonstrated non-uniform variation in texture, which the authors attributed to limited fixation stability of the test subject.[88] Rosenfeld et al reported a novel use of en-face image processing algorithm for identifying areas at risk of geographic atrophy (GA) progression, in their study, darker areas on the en-face slab images of the EZ correlated with areas that developed GA, suggesting that EZ disruption may represent an early defect preceding GA.[89] Although to date, there is no reported study investigating the change in the EZ intensity on en-face OCT, a volumetric analysis of the EZ or a measure of overall intensity, might have the potential to become a surrogate measure of disease severity in AMD and other retinal conditions.

Current Limitations and Future Direction

The advancement in OCT technology has resulted in improved scan resolution, speed and signal-to-noise ratio which has translated into better delineation of subtle changes of retinal ultrastructures secondary to disease pathology. As this field is ever evolving due to new innovation in imaging techniques, clinicians who utilize OCT in their daily practice for clinical decision-makings must also be aware of the current limitation of this relatively new technology.

Although SD-OCT is capable of resolving the different layers of the retina, it lacks the lateral resolution to resolve cellular details of each layer.[46] Newly emerged imaging techniques such as adaptive optics have been shown to combine both cellular lateral resolution and depth resolution offered by the conventional SD-OCT.[35,]

[41, 90] Consequently, previously proposed anatomical correlates are being questioned in newer studies and as such we should remain open to the need to re-evaluate our current assumptions on anatomical correlates to the bands and the zones seen on OCT.

Commercially available OCTs do not display the raw linear data due to the large amount of back-scattered light captured in generating the native images. Final images are usually produced from transformation of the linear OCT data through combination of logarithmic or root transformation.[91] Furthermore, the SD-OCT final output image is both dependent on and limited by the instrument's ability to resolve physical structural details, also known as the point spread function of the instrument. The axial dimension of an imaged object is therefore dictated by the axial resolution of the instrument itself. For example, an infinitely thin hypothetical reflector when imaged by an OCT would have appeared as thick as the point spread function of the instrument,[91] and in case of the Spectralis SD OCT, it would appear as a hyper-reflective band measuring at 7 microns. Therefore, the final OCT images may misrepresent actual difference in reflectivity.[1, 12]

There are always further improvements in imaging, such that now with swept source OCT (SS-OCT) we can visualize deep structures in the posterior pole such as the choroid and therefore allow the ability to assess differences in choroidal structure with disease.[24, 92-94] More recently there are devices that combine OCT imaging with angiography allowing blood vessels and flow to be determined without the need for formal fluorescein and indocyanine green angiography. With ever evolving techniques we are sure to learn more about the ultrastructure and vasculature of the retina and choroid, and their changes in different eye conditions.

CONCLUSION

The second hyper-reflective band on SD-OCT is currently referred as the ellipsoid zone. Although there is still a lack of a consensus on the exact anatomical correlate of the EZ, the integrity and intensity of the EZ has been shown to be associated with the visual function and is an important indicator of visual outcomes in many retinal conditions. With a relatively quick and highly reproducible OCT image acquisition, the integrity and intensity of the EZ has the potential for assessing the health of the outer retina in clinical and research settings.

Method of Literature Search

References for this review were identified through a comprehensive literature search of the following electronic databases: MEDLINE, PubMed, and Science Direct. In addition, articles, textbooks, and thesis thought to be relevant were also selected from review of the bibliographies of those articles generated from the above search. The following keywords and combinations of these words were used in compiling the search: "optical coherence tomography", "second hyper-reflective band", "IS/OS junction", "inner segment ellipsoid", "integrity" and "intensity".

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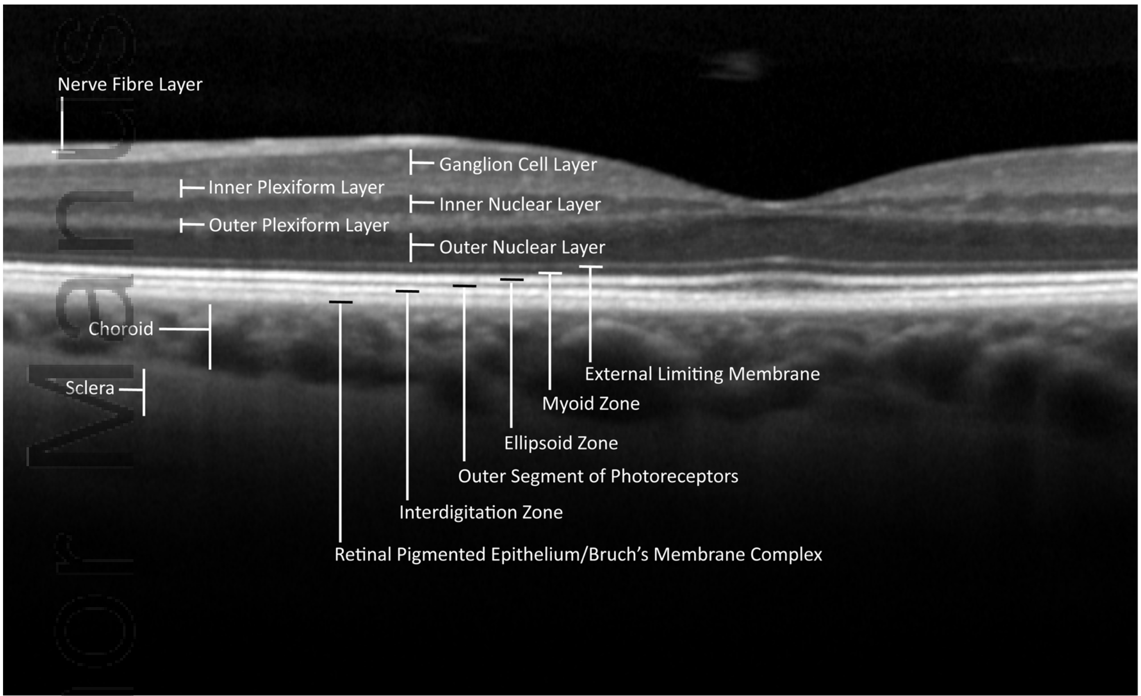
FIGURE LEGENDS

Figure 1: An example of a SD-OCT of a normal eye.

Figure 2: OCT images and mfERG responses from an intermediate AMD eye. OCT scans show drusen regression and change in the EZ integrity at the 12-month visit, and the recovery of the EZ integrity at the 24-month visit. The recovery of the EZ integrity is associated with the improvement in the mfERG implicit time, particularly at the central and temporal retina.

Figure 3: Fundus autofluorescence (FAF) and OCT images of an eye with MEWDS. The OCT image shows the disruption of the EZ (arrows) at the lesion.



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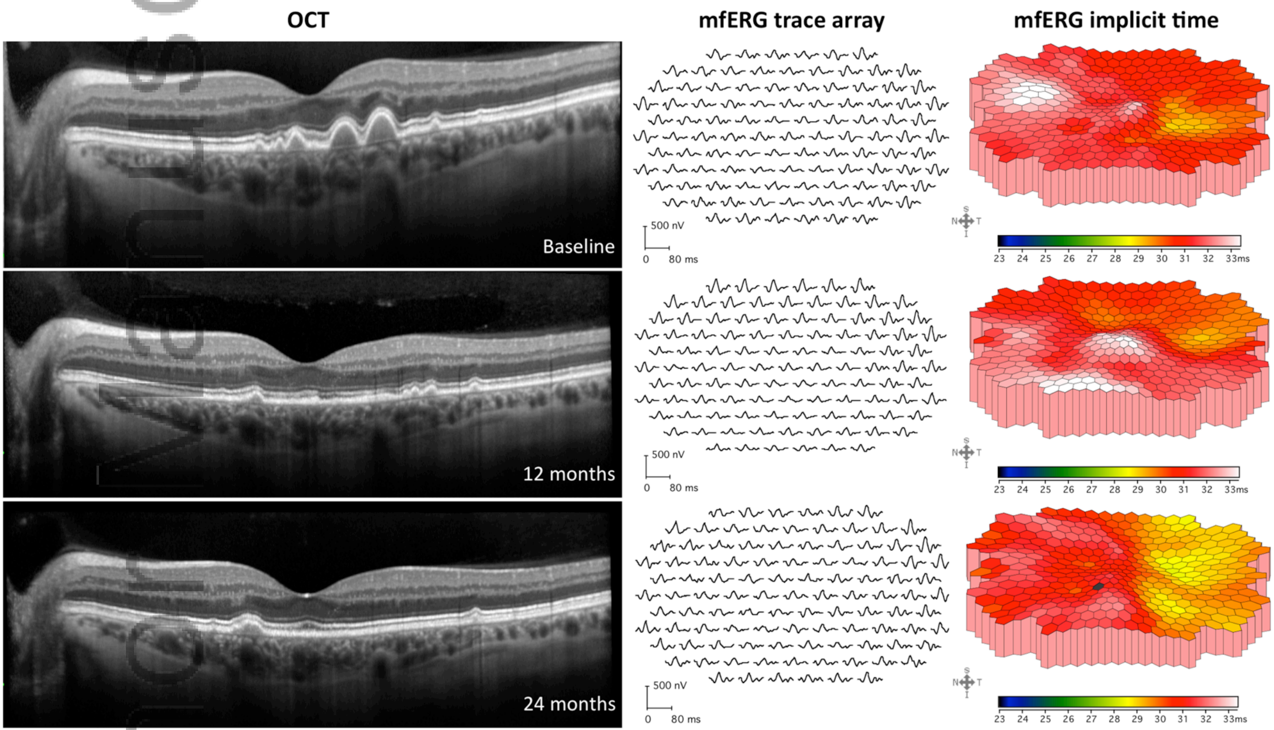

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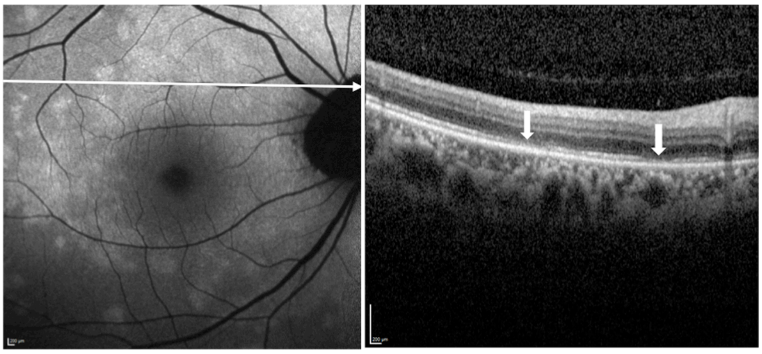

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