Focus on external limiting membrane and ellipsoid zone in diabetic macular edema

There are over 93 million people with diabetic retinopathy (DR) worldwide. Over 21 million demonstrate evidence of diabetic macular edema (DME).[1] Advances in spectral-domain optical coherence tomography (SD-OCT) have enhanced the appreciation of morphological alterations in individual layers of the retina in DME, including the external limiting membrane (ELM) and photoreceptor ellipsoid zone (EZ). SD-OCT-based macular thickness parameters, ELM, and EZ disruption have been defined as imaging biomarkers for the severity of DR. They have been found to correlate with an increase in vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 (ICAM-1), the angiogenic and inflammatory mechanisms involved, respectively, in the pathophysiology of the disease.[2-5] Despite advancements, ELM and EZ assessments remain inadequate in DME evaluation in clinical practice.

Advancements in structural-OCT technology helped define the four components of the outer retina. Spaide and Curcio reviewed the literature concerning the histology of the outer retina and used data to create a scale model drawing. They highlighted that the first, innermost band and the fourth, outermost band corresponded with the ELM and the retinal pigment epithelium (RPE), respectively. The third band matched to an ensheathment of the cone's outer segments by apical processes of the RPE. However, their comparative analysis revealed that the second band, often attributed to the boundary between inner and outer segments of the photoreceptors, aligned with the ellipsoid portion of the inner segments.[6] Although there has been some controversy regarding the precise origin of this boundary, the term "ellipsoid zone" (EZ) was recommended as a compromise term by the International OCT consensus panel.[7] The status of ELM and EZ has also been evaluated in brown Norwegian rats. It was found that the EZ and ELM disappeared or reduced in reflectivity after euthanasia. The origin of the EZ and ELM was considered to be related to the biological activities of the photoreceptor cells.[8]

The ELM and EZ can be visualized exquisitely on SD-OCT. The ELM separates the layers of rods and cones from the overlying outer nuclear layer and is a linear confluence of junctional complexes between Muller cells and photoreceptors. It has been demonstrated in rat and monkey retina that tight junctions (TJs) exist in the ELM. Occludin, a protein, has been found to be a key component of TJs.[9] Occludin has a significant role in the regulation of barrier properties of ELM. It is noteworthy that VEGF induces phosphorylation-dependent occludin ubiquitination and alters TJs.[10] The EZ clinically defines the photoreceptor integrity. The biological ellipsoid consists mainly of mitochondria, enabling higher levels of energy consumption within the photoreceptors. The focal or global absence of the EZ corresponds with the reduced reflectivity or anatomic absence of the EZ. EZ disruption has also been found to correlate with the presence of disorganization of retinal inner layers (DRIL) and an increase in the resistive index of the central retinal artery on color Doppler imaging.[11,12]

The ELM and EZ integrity is essential for the maintenance of vision.[13] DME is known to be associated with disruption of ELM and EZ, which in turn affects visual acuity.[14] Mechanisms of ELM and EZ disruption have been highlighted in DME. Accordingly, disruption of ELM and EZ has been graded as grade 0: no disruption of ELM and EZ present; grade 1: ELM disrupted but EZ intact; and grade 2: both ELM and EZ disrupted. This physician-friendly grading system shows an excellent reproducibility and is an important predictor of disease level and visual outcome. The disruption scale correlates significantly with logMAR visual acuity (VA).[3] The integrity of ELM and EZ has been found to be a positive predictor for visual outcomes. The EZ disruption has also been graded as grade 0: intact EZ; grade 1: focal disruption (subfoveal EZ); and grade 2: global disruption (EZ involving macular cube).[15]

Advancements in OCT angiography technology have enhanced the understanding of the retinal vasculature and ELM and EZ integrity. Correlations between baseline deep capillary plexus (DCP) integrity parameters (vascular flow density [VD] and area of the foveal avascular zone [FAZ]) and photoreceptor ELM and EZ integrity have been analyzed. The degree of EZ and ELM integrity recovery has been found to correlate well with the baseline DCP VD and DCP FAZ. Compared with anti-VEGF nonresponders, anti-VEGF responders have higher baseline DCP integrity and a significantly greater degree of photoreceptor recovery. The degree of DCP preservation at the time of initial DME resolution correlates closely with long-term recovery of photoreceptor integrity and visual outcome in patients with resolved DME.[16]

In DME, anti-VEGFs and intravitreal steroids remain the mainstay of treatment. Administration of intravitreal anti-VEGF agents has been found to be associated with a reduction in CST and improvement in VA. Mechanism of ELM and EZ restoration has been highlighted recently in DME. Anti-VEGF therapy results in restoration of the barrier effect of ELM. The ELM has been observed to restore first followed by EZ restoration. Increase in VA is more pronounced in patients associated with restoration of ELM and EZ.[17] Intravitreal ranibizumab has been found to restore foveal photoreceptors in DME.[4] Improvement in photoreceptor integrity occurs after the second and third dose of ranibizumab with improvement in VA. A larger foveal photoreceptor microstructure defect is associated with lower VA. Cases with larger foveal photoreceptor microstructure defects at baseline have lesser VA improvements.[18] Intravitreal dexamethasone implant has been found to significantly improve ELM and EZ integrity in naïve patients with retinal vascular disease.[19] Repeated intravitreal dexamethasone implants have been found to be of value in patients with DME refractory to anti-VEGF therapy. The ELM and EZ disruption decreases after the first injection and remains stable after the second injection.[20]

In conclusion, evaluation of ELM and EZ is essential, besides analysis of macular thickness parameters, in DME. While evaluating DME on structural OCT, the status of ELM and EZ should be considered for clinical decision-making,

timing of therapeutic intervention, and prognostication and management of disease.

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