Ellipsoid Zone Change According to Glaucoma-Stage Advancement

EDITOR:

THE FINDINGS OF HA AND ASSOCIATES[1] OF REDUCED RELATIVE ellipsoid zone (EZ) intensity in spectral-domain optical coherence tomography (SD-OCT) scans in more advanced stages of glaucoma are of great interest. The authors speculate elegantly regarding possible mechanisms, including trans-synaptic retrograde degeneration or Müller cell dysfunction, leading to alterations in photoreceptor mitochondria. One issue that deserves consideration is potential confounding owing to optical effects. It is a common finding on SD-OCT that an overlying hyperreflective structure (such as a blood vessel[2] or exudate[3]) will result in a shadowing effect, whereby the reflectivity of structures underneath is diminished. Similarly, incremental loss of the overlying ganglion cell and nerve fiber layer, as occurs in more advanced glaucoma, would be expected to incrementally increase the intensity of the EZ and the external limiting membrane (ELM).

The authors calculated relative intensity by dividing EZ intensity by that of the ELM, as described in a recent study evaluating these bands in intermediate age-related macular degeneration (AMD).[4] However, it is plausible that an equal increase in intensity of both bands, owing to loss of the overlying ganglion cell complex, will result in a numerically smaller relative EZ intensity. For example, if, using arbitrary intensity units, the intensity of the EZ is 3 and the intensity of the ELM is 1, the relative EZ intensity will be 3. Supposing that, after loss of overlying reflective structures, the intensity of both lines increases by 0.2 units (giving intensities of 3.2 and 1.2 for EZ and ELM, respectively), the relative EZ intensity then appears to fall, as the ratio is now 2.67. In fact, it can be shown mathematically that any absolute (not proportionate) increase in reflective intensity that is the same for both the EZ and ELM will result in an apparent increase in relative EZ intensity, provided the EZ intensity is greater than ELM intensity, which is indeed the case. Such an effect would not occur in the AMD investigation,[3] as in that study the structural alterations are beneath (more scleral to) the photoreceptors and so would not cause a shadowing effect.

Thus, it is possible that the findings of the glaucoma study[1] could be explained, at least partly, by optical factors without retrograde degeneration. It would be useful to know the absolute intensities of the EZ and ELM lines, prior to calculating the ratio, in the different groups. Other methods of adjustment could be attempted, such as first subtracting any absolute increase in ELM intensity from the EZ value, or dividing instead by the intensity of the retinal pigment epithelium line (which is of a more comparable intensity to the EZ line), to see if the findings differ. Nevertheless, we applaud the authors for raising the possibility of trans-synaptic degenerative processes and Müller cell dysfunction in this condition.

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REPLY

WE APPRECIATE THE COMMENTS FROM MAHROO AND ASSOciates regarding our recently published article. Our study demonstrated relative ellipsoid zone (EZ) intensity reduction in the mild-to-moderate and severe glaucoma stages on spectral-domain optical coherence tomography (SD-OCT), and the extent of reduction was positively associated with glaucoma severity.

We are in total agreement with the point noted, that incremental loss of the overlying ganglion cell and nerve fiber layer would incrementally increase the intensity of both the EZ and the external limiting membrane (ELM). We would like to emphasize, however, that the degree of intensity increase is more likely to be *proportional* in both bands.

As light passes through media, its intensity decreases exponentially according to the depth of the media, as follows[1]:

$$I_{(z)} = I_0 e^{-\alpha z}$$

where α is a constant determined by the optical property of the media, and z is the depth of the media. After the light is reflected from the ELM (or EZ) and passes back through the media again, its intensity as detected by the OCT detector can be represented as:

$$I_D = I_0 \Gamma e^{-2\alpha z}$$

where Γ is the reflectivity of the target layer.[1] Assuming a retinal thickness change from z_1 to z_2, the intensity of the light reaching the OCT detector would be altered from $I_0 \Gamma e^{-2\alpha z1}$ to $I_0 \Gamma e^{-2\alpha z2}$, the ratio of which is constant ($e^{-\alpha(z2-z1)}$). As this ratio is independent of the target layer, its value would be the same in the ELM and EZ. Therefore, as the ganglion cell and nerve fiber layer thickness decreases, the intensity in the EZ and ELM would increase proportionally.

This modeling is based on the assumption that the wavelength of light that is reflected from the ELM and EZ is exactly the same. Also, we neglected the depth difference between the ELM and EZ. Obviously, the optical effects of the loss of the ganglion cell and nerve fiber layer on the intensity of the EZ should be investigated in future studies. However, we do not think that the findings would change the core message of our study.

We hope that our study will foster further and lively discussion on photoreceptor changes in glaucoma as well as continued evaluation of its clinical significance. We thank Mahroo and associates again for their thoughtful suggestions, and we do look forward to comparing the results obtained using different methods and references on EZ intensity analysis.

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Randomized, Controlled, Phase 2 Trial of Povidone-Iodine/ Dexamethasone Ophthalmic Suspension for Treatment of Adenoviral Conjunctivitis

EDITOR:

I HAVE READ THE MANUSCRIPT ENTITLED "RANDOMIZED, Controlled, Phase 2 Trial of Povidone-Iodine/ Dexamethasone Ophthalmic Suspension for Treatment of Adenoviral Conjunctivitis" by Pepose and associates, published in your journal.[1] The authors use a novel drug combination in the treatment of adenoviral conjunctivitis and they suggest that this combination is safe and effective clinically in humans. After reading the paper, I want to add a comment regarding exclusion criteria of the study. Hyperthyroiditis is a hormone and iodine metabolism disorder. Hyperthyroiditis patients should be limited as to consumption of and contact with iodine compounds for preventing aggravation or reactivation of the diseases. For that purpose the patients should use salt without iodine in foods, and health workers should use disinfectants without iodine components during any medical intervention or surgery. In the current study, a combination eye drop is used 4 times a day for 5 days that contains 0.6% iodine. Eye drops may be absorbed via the conjunctival and lacrimal system after instillation and may affect the patient systemically. For this reason, I believe that the exclusion criteria should include hyperthyroiditis disease in the study. Doctors who will use this combination in their patients' treatment for adenoviral conjunctivitis should ask the patients about hyperthyroiditis. Thank you very much.

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REPLY

WE WOULD LIKE TO THANK DR CINAL FOR HIS INTEREST IN our article and welcome the opportunity to respond to the points made in his letter.

In our study,[1] patients with hyperthyroidism were not excluded as the risk of systemic exposure to iodine following topical ophthalmic administration of povidone-iodine (PVP-I) 0.6%/dexamethasone 0.1% is expected to be minimal. We should note that the formulation used in our study contained 0.6% PVP-I and not 0.6% iodine as stated by Dr Cinal. Most of the iodine in PVP-I is complexed with the povidone carrier, whereas a small amount of free iodine is released in equilibrium with the complex.[2]

Two studies have evaluated the exposure to iodine after single topical ocular administration of PVP-I in adult patients being prepared for cataract surgery.[3,4] In a study in which the ocular surface of 19 cataract patients was