Relationship between Retinal Microstructures on Optical Coherence Tomography and Microperimetry in Age-Related Macular Degeneration

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Purpose: To determine the relationship between structural parameters of the outer retina on spectral-domain optical coherence tomography (SD-OCT) and microperimetric retinal sensitivity in early stages of age-related macular degeneration (AMD).

Design: Prospective, observational study.

Participants: Seventy-five eyes of 75 participants with early stages of AMD (drusen $\geq$125 μm, with/without pigmentary abnormalities) and 25 control participants of a similar age.

Methods: Participants underwent microperimetry testing and high-resolution SD-OCT scans. Structural parameters at 5 central points (0°, 1°, and 2.33° nasal and temporal to the fovea along the horizontal axis) corresponding to areas tested by microperimetry were compared. Structural parameters included outer segment (OS) length, thickness and elevation of the retinal pigment epithelium (RPE) band, grading of the inner-segment ellipsoid (ISe) band integrity, and presence of hyperreflective foci (HF).

Main Outcome Measures: Relationship between structural parameters and retinal sensitivity.

Results: Retinal sensitivity was significantly correlated with RPE elevation ($P < 0.001$), ISe grading ($P < 0.001$), and presence of HF ($P \leq 0.018$) at all test points, but not with OS length ($P \geq 0.093$) or RPE thickness ($P \geq 0.125$). However, multiple linear regression analyses revealed that only ISe grading ($P \leq 0.011$) and RPE elevation ($P \leq 0.030$) remained significantly associated with retinal sensitivity at all points. By using a simple linear model incorporating ISe grading and RPE elevation to predict values of retinal sensitivity, the 95% limits of agreement between the predicted and the actual value was ±3.83 dB.

Conclusions: The integrity of the ISe band and drusen-associated RPE elevation are significant independent predictors of microperimetric retinal sensitivity. Our findings imply that these 2 structural parameters may be surrogate markers of retinal function in the early stages of AMD. *Ophthalmology 2014;■:1–8 © 2014 by the American Academy of Ophthalmology.*

A major impediment to the evaluation of novel interventions and treatments for the early stages of age-related macular degeneration (AMD) is the lack of sensitive and clinically applicable markers that can be used as surrogate clinical trial end points. These markers are required because the natural progression of the early stages of AMD is slow, with traditional functional end points such as visual acuity often remaining unaffected for years after a diagnosis of AMD has been made. By the time visual acuity is affected, significant pathologic changes have already occurred.

The advent of high-resolution optical coherence tomography (OCT) has allowed visualization of pathologic details not previously possible with color fundus photography and has provided a new opportunity for identifying novel structural markers of disease. Structural changes that have been investigated in early stages of AMD include changes in photoreceptor layer thickness,[1–4] inner-segment ellipsoid (ISe) band integrity[5–8] and intensity,[9,10] drusen area and volume,[11–13] and presence of hyperreflective foci (HF).[14–16] Although these structural changes may be effective biomarkers used to determine severity of disease, an ideal biomarker that could be used as a surrogate end point in AMD clinical trials is one that would also reflect changes in visual function.[17] Therefore, it is essential that we establish the relationship between these structural changes and visual function.

Fundus-tracked microperimetry has recently been used to determine visual function in several retinal diseases,[18–27] because it can sensitively and topographically detect functional changes often missed or underestimated by visual acuity. In AMD, microperimetry has been explored as a useful functional measure in advanced AMD,[18,20,21,27] and previous studies have also found functional deficits in the early stages of AMD.[28–30] Further investigations have found significant correlations between microperimetric retinal sensitivity and retinal microstructures, such as the thickness of the photoreceptor outer segment (OS),[4] integrity of the ISe band,[6,8] and drusen volume.[6] However, no study to date has examined the association between HF and retinal sensitivity, nor has one study looked at all these potential structural markers

ISSN 0161-6420/14/$ - see front matter
http://dx.doi.org/10.1016/j.ophtha.2014.01.025

collectively to determine their relative contribution to functional alteration in a robust statistical model. The knowledge of their relative contribution will allow a better understanding of which structural parameters, or combinations, affect retinal function.

The ability to measure visual function is highly desirable when considering the efficacy of any intervention. However, the subjective measurement of visual function with techniques such as microperimetry will by its very nature be variable,[31] whereas the determination of structural parameters identified on high-resolution imaging provides rapid assessment in an objective manner. By determining structure–function relationships, robust structural biomarkers of disease severity will be identified. They may also identify eyes at risk of developing advanced AMD, because we have previously found that areas with progressive reduction in retinal sensitivity predicted the development of localized geographic atrophy (GA).[32] Therefore, the purpose of this study was to determine the correlation of structural changes visualized using high-resolution OCT with microperimetric retinal sensitivity.

Methods

This study was approved by the Human Research Ethics Committee of the Royal Victorian Eye and Ear Hospital and was conducted in accordance with the Declaration of Helsinki; written informed consent was obtained from all participants.

Participants

Participants were recruited from the Macular Research Unit, Centre for Eye Research Australia, as part of a natural history study of AMD. Participants aged 50 years or more and with best-corrected visual acuities of ≥20/40 were recruited for this study. The inclusion criteria for AMD participants were drusen ≥125 μm with or without pigmentary abnormalities (intermediate AMD[33]) for both eyes, with 1 eye randomly selected as the study eye by random allocation using computer-generated numbers. Exclusion criteria for any study eye included the presence of choroidal neovascularization, any GA, significant cataracts, glaucoma, amblyopia, or any corneal pathology that would compromise vision. Participants were also excluded if they had diabetes, had any neurologic or systemic disease affecting vision, were taking any medication known to affect retinal function, had any physical or mental impairment preventing them from participating in this study, or were unable to sign a consent form.

Spouses and friends of the participants were recruited as control participants for this study to provide normative data for visual function tests. Control participants were included only if there were no signs of AMD, including reticular pseudodrusen, in either eye, although drusen ≤63 μm were allowed (normal aging changes).[33] The exclusion criteria for the control participants were the same as for the AMD participants.

Microperimetry Examination

Microperimetric examination was performed using the Macular Integrity Assessment (CenterVue, Padova, Italy) microperimeter on all participants before performing any tests that could significantly bleach the photoreceptors (e.g., fundus autofluorescence or fundus photography). Pupillary dilation was performed on all participants using 1 drop of 1% tropicamide and 1 drop of 2.5% phenylephrine to achieve a pupil diameter of at least 6 mm. Identical instructions were given to all participants regarding the microperimetry examination. A customized stimulus grid (Centre for Eye Research Australia AMD 6^0 grid) was designed specifically for the assessment of the macular region, consisting of 37 points located at 0°, 1°, 2.33°, 4°, and 6° from fixation (Fig 1). Test reliability was assessed by the frequency of false-positive responses to suprathreshold stimuli presentations to the optic nerve head (blind spot), and any participant with false-positive responses >25% on any examination was excluded from this study. Details of microperimetric examinations have been outlined in greater detail by Wu et al.[34]

During 1 session, 3 consecutive examinations were performed on 1 study eye for AMD participants and 2 consecutive examinations were performed on 1 study eye for control participants. All participants were given a few minutes of rest between each test to minimize the effect of fatigue on the test. The first examination was discarded for all participants to minimize learning effect and test–retest variability,[34] with results for the 2 subsequent microperimetry examinations in AMD participants averaged to increase the accuracy of the measured value at each point. For the purpose of studying localized structure–function relationships at the macula, microperimetric retinal sensitivity of only the 5 points along the horizontal meridian (2.33° nasal, 1° nasal, 0° central, 1° temporal, and 2.33° temporal) was analyzed, because angioscotomas that interfere with the interpretation of these results are unlikely to occur within this region.

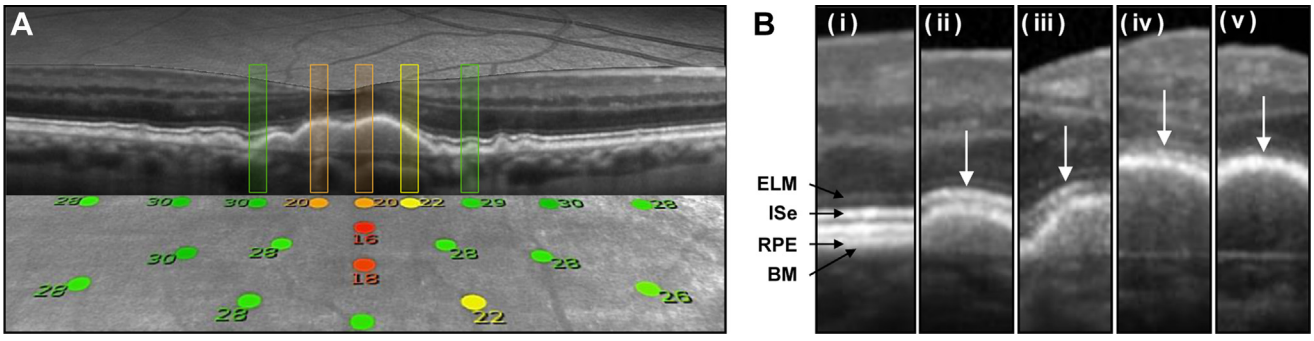

Figure 1. Measurements on spectral-domain optical coherence tomography (SD-OCT). **A,** Horizontal B-scan is shown with the 5 regions analyzed that correspond with the areas tested on microperimetry. **B,** Grading of inner-segment ellipsoid (ISe) band integrity; (i) SD-OCT B-scan of normal participant is shown, with corresponding layers labeled: external limiting membrane (ELM), ISe, retinal pigment epithelium (RPE), and Bruch's membrane (BM). Shown are the SD-OCT scans of participants with age-related macular degeneration (AMD) with an ISe integrity grading of (ii) grade 0, no disruption; (iii) grade 1, <50% disruption; (iv) grade 2, >50% disruption; and (v) grade 3, complete absence of ISe line.