Longitudinal Changes in Microperimetry and Low Luminance Visual Acuity in Age-Related Macular Degeneration

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IMPORTANCE There is a need for more sensitive measures of disease in intermediate age-related macular degeneration (AMD) to evaluate novel interventions more effectively and expediently.

OBJECTIVE To determine if microperimetry and low luminance visual acuity can detect functional changes over a short duration of follow-up.

DESIGN, SETTING, AND PARTICIPANTS Prospective longitudinal examination of 49 participants with consecutive AMD and 10 healthy participants in a research clinic from May 1, 2012, to December 31, 2013. Forty-one participants had intermediate AMD, 8 had nonfoveal geographic atrophy due to AMD. Participants underwent microperimetry examinations in 1 eye during a 12-month period at 6-month intervals for participants with AMD and at baseline and 12 months for control participants; low luminance visual acuity was performed at baseline and at 12 months for all participants. Changes in pathological features of intermediate AMD eyes were determined using side-by-side comparisons of color fundus photographs from the initial and final visit as remaining stable, progressed, or improved.

MAIN OUTCOMES AND MEASURES Microperimetric sensitivity and low luminance visual acuity.

RESULTS A reduction in mean (SE) microperimetric pointwise sensitivity was identified at 12 months compared with the baseline for intermediate AMD eyes graded as stable (−0.31 dB [0.10 dB]; P = .003) or worsened (−0.42 dB [0.12 dB]; P < .001) and an improvement in mean (SE) pointwise sensitivity was identified in eyes graded as improved (1.13 dB [0.23 dB]; P < .001). A reduction in mean (SE) pointwise sensitivity was identified in eyes with nonfoveal geographic atrophy at both 6 months (−1.41 dB [0.22 dB]; P < .001) and 12 months compared with the baseline (−2.56 dB [0.22 dB]; P < .001) while a change in mean (SE) pointwise sensitivity was not identified over the 12-month period for control participants (−0.11 dB [0.11 dB]; P = .34). No changes in best-corrected visual acuity or low luminance visual acuity were identified in all groups over the 12-month period (P ≥ .07).

CONCLUSIONS AND RELEVANCE Microperimetry detected subtle changes in visual function over a 12-month period in eyes with intermediate AMD but visual acuity measures did not identify any such changes. These findings suggest that microperimetry is worth exploring as a method for assessing the efficacy of novel interventions for intermediate AMD potentially requiring a shorter duration of follow-up.

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The hallmark clinical signs of age-related macular degeneration (AMD) in its early stages are the presence of drusen and pigmentary change in the macula, which can be present for many years prior to the development of vision-threatening complications. Significant progress has been made in understanding the pathogenic pathways involved in AMD and, as such, novel intervention strategies in the early stages of AMD are currently being developed or trialed.

To evaluate these early interventions more effectively, there is a need for more sensitive and effective biomarkers because the most commonly used measure of best-corrected visual acuity (BCVA) is not useful in the early stages of AMD. Many other measures of retinal function have been explored in the early stages of AMD and have the potential to serve as such functional biomarkers of the disease. Among them is the measure of sensitivity to luminance increments using microperimetry and the measure of low luminance visual acuity (LLVA).

Microperimetry has been used in the atrophic and neovascular stages of AMD. In addition to other studies, we have shown that microperimetry can sensibly measure functional deficits in the early stages of AMD in a repeatable manner. However, to our knowledge, no longitudinal study to date has examined whether microperimetry is useful for monitoring disease progression in the earlier stages of AMD.

Low luminance visual acuity is another measure that is rapid and simple to perform. It has been shown previously in eyes with nonfoveal geographic atrophy (GA) that low luminance deficit (LLD; the difference between LLVA and BCVA) is predictive of subsequent vision loss and enlargement of the GA area. Although it has been suggested that LLVA may be an effective measure in the early stages of AMD, we did not find LLVA to be more useful than BCVA as a functional measure in the early stages of AMD in a recent study. However, it has not been determined whether LLVA is more effective longitudinally as a functional measure and whether the measure of LLD conveys any prognostic value in the early stages of AMD.

In this study, we examined longitudinal changes in microperimetric sensitivity and LLVA over a 12-month period in participants with intermediate AMD.

Methods

Ethical approval was obtained from the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital and the study was conducted in adherence with the Declaration of Helsinki. An explanation of all tests involved in this study was provided prior to obtaining written informed consent from all participants.

Participants

Participants were recruited from the Macular Research Unit at the Centre for Eye Research Australia as part of a natural history study of AMD. The inclusion criteria for all participants in this study included being 50 years or older and having a BCVA of 20/40 (0.30 logMAR) or better in the study eye. The inclusion criteria for study eyes with intermediate AMD included having drusen 125 μm or larger, with or without pigmentary changes. Eyes with nonfoveal geographic atrophy (GA) due to AMD were also included. Spouses and friends of the participants with AMD of a similar age without any signs of AMD in either eye (the presence of drusen <63 μm were allowed) were included as control participants. For participants with AMD and control participants, the eye with the better visual acuity was designated as the study eye if both eyes met the inclusion criteria. The exclusion criteria for any study eye included the presence of GA involving the fovea; choroidal neovascularization; glaucoma; significant cataract; any corneal pathology that could compromise vision; diabetes mellitus; uncontrolled hypertension, amblyopia, neurologic, or systemic disease affecting vision; or any medication known to affect retinal function. Participants were also excluded if they had any physical or/and mental impairment preventing them from participating in this study or an inability to sign a consent form. All participants with AMD were seen at 3 visits during a 12-month period at 6-month intervals and all control participants were seen at 2 visits (baseline and 12 months); participants who were unable or unwilling to participate in the entire length of the study were also excluded.

Procedures

All participants first performed visual acuity measurements then microperimetric examinations followed by multimodal imaging and clinical examination by a senior retinal specialist during each visit. Multimodal imaging included color fundus photography (CFP), near-infrared reflectance, short-wavelength fundus autofluorescence, and spectral-domain optical coherence tomography line and volume scans on a Spectralis HRA+OCT (Heidelberg Engineering).

Visual Acuity Measurements

Best-corrected visual acuity measurements were performed monocularly following a standardized refraction protocol using an Early Treatment of Diabetic Retinopathy Study refraction chart at 4 m. Low luminance visual acuity was measured using a 2.0-log unit neutral density filter (Wratten filter; Kodak) placed in front of the eye, as previously outlined. Participants were required to guess all the letters in a given line and measurements were recorded as the number of letters read and the logMAR value, with each letter given a score of 0.02 logMAR. The difference between LLVA and BCVA was then used to derive the measure of LLD. Visual acuity measurements were performed during the first and third visits (ie, at baseline and 1-year follow-up visits).

Microperimetric Examination

The Macular Integrity Assessment microperimeter (CenterVue) was used to examine all participants using a procedure that has been outlined in detail in a previous study. A detailed description can be found in eAppendix 1 in the Supplement. A customized stimulus grid (Center for Eye Research Australia; AMD 6°-grid), consisting of 37 points located at 0°, 1°, 2.33°, 4°, and 6° from fixation, was used in?
In this study, 2 consecutive examinations during each visit were performed on the study eye for all participants, with approximately 3 minutes of rest given between each test to minimize the effect of fatigue. Test reliability for the second examination was assessed by the frequency of false-positive responses measured by presentations of suprathreshold stimuli to the physiological blind spot, which was manually located on the microperimeter before the presentation of the first stimuli. Any test with false-positive responses greater than 25% was considered unreliable and was repeated. This cutoff was chosen because the microperimeter presented a false-positive stimulus approximately every 1 minute and there were typically only 4 to 5 false-positive stimuli presented in each test given the short duration of the examinations.

**Fundus Photography Assessment**

A senior retinal specialist (R.H.G.) and an experienced grader (Z.W.), both masked to the results of microperimetry, independently determined if there were changes in the severity of the clinical features seen on CFP over the course of the follow-up. Using side-by-side evaluations of the CFP between visits, the development or disappearance of drusen and/or pigmentary changes or a change in drusen area without the development of advanced AMD (such as the development of GA with drusen regression) was used to determine if an eye had clinically progressed or improved, respectively. An eye was considered to have remained stable if these AMD features remained unchanged. Any disagreement on the grading was resolved by open adjudication between the 2 graders. The development of advanced AMD was confirmed with additional clinical examination and retinal imaging in the clinic.

**Statistical Analysis**

The full details of the statistical analyses in this study are in eAppendix 2 in the Supplement.

**Results**

A total of 49 participants with consecutive AMD (41 with intermediate AMD and 8 with nonfoveal GA) and 10 control participants who met the inclusion criteria were included in this study and a summary of their characteristics and length of follow-up is shown in the Table. The participants with intermediate AMD, nonfoveal GA, and the control participants had mean (SE) ages of 68.8 years (9.2 years), 69.1 years (6.8 years), and 66.0 years (3.5 years), respectively.

**Intrasession Test-Retest Characteristics Over 3 Visits**

Of the total of 49 participants with AMD in this study, 39 participants (68.1 years [7.8 years]; range, 53-87 years) had not performed microperimetry prior to their first visit. Linear mixed
effects models revealed an increase in mean (SE) pointwise sensitivity (PWS) between the 2 examinations during the first visit (0.33 dB [0.06 dB]; P < .001) but a change was not identified during the second and third visits (0.10 dB [0.07 dB]; P = .14 and −0.02 dB [0.07 dB]; P = .79, respectively). Therefore, the first examination during the first visit for all participants in the subsequent analyses was discarded and the second examination was used; the first examinations for the second and third visits were used because there were no intrasession changes observed in mean PWS.

**Longitudinal Changes in Microperimetric Sensitivity in Different Groups**

For the control participants, a change in the mean (SE) PWS from baseline to the 12-month visit was not identified (−0.11 dB [0.07 dB]; P = .34). In the 41 eyes with intermediate AMD, 46%, 37%, and 15% of the eyes had clinical features that were graded as stable, progressed, or had improved by the third visit, respectively. One eye developed choroidal neovascularization by the third visit and was excluded from subsequent analyses but no eyes developed GA. Of interest, the microperimetric sensitivity of this participant did not appear distinctly different from the other participants in this study during the visit prior to the development of choroidal neovascularization.

In the eyes that were graded as having progressed, a reduction in the mean (SE) PWS was not identified by the second (6-month) visit compared with the baseline (−0.18 dB [0.12 dB]; P = .13) but was identified by the third (12-month) visit compared with the baseline (−0.42 dB [0.12 dB]; P < .001). Similarly, a reduction in the mean (SE) PWS in eyes graded as remaining stable was not identified by the second visit compared with the baseline (−0.08 dB [0.10 dB]; P = .45) but was identified by the third visit compared with the baseline (−0.31 dB [0.10 dB]; P = .002). For eyes that were graded as having improved, a change in the mean (SE) PWS was not identified by the second visit compared with the baseline (0.42 dB [0.23 dB]; P = .07) but an increase was identified by the third visit compared with the baseline (1.13 dB [0.23 dB]; P < .001). For the eyes with nonfoveal GA, a reduction in the mean (SE) PWS from the baseline was identified during the second and third visits (−1.41 dB [0.22 dB]; P < .001 and −2.56 dB [0.22 dB]; P < .001, respectively; Figure 1).

To examine the changes in microperimetric sensitivity for stimulus points grouped by different eccentricities, eyes with intermediate AMD that either remained stable or progressed by the third visit were analyzed because they exhibited a reduction in the mean (SE) PWS. From these 34 eyes, linear mixed effects models revealed a reduction in mean (SE) PWS for rings 2 (2.33°; −0.61 dB [0.16 dB]; P < .001) and 3 (4°; −0.37 dB [0.13 dB]; P = .005), but a reduction in the mean (SE) PWS was not identified in rings 1 (0° and 1°; −0.47 dB [0.25 dB]; P = .06) and 4 (6°; −0.11 dB [0.13 dB]; P = .54) by the third visit; no change in mean PWS was identified in any ring by the second visit (P > .10; Figure 2). We did not find a difference in the longitudinal changes in microperimetric sensitivity when repeating the analyses multiple times for 5 randomly selected points in rings 2 and 3 and therefore considered it unlikely that the absence of a change in ring 1 was owing to the fewer points present in that ring (data not shown).

**Longitudinal Changes in Visual Acuity Measures**

Changes in either mean (SE) BCVA or LLVA were not identified for the control eyes (−2.1 letters [3.6 letters]; P = .58 and −2.3 letters [3.9 letters]; P = .58, respectively), eyes with intermediate AMD that remained stable or progressed (−1.2 letters [0.7 letters]; P = .07 and −0.8 letters [1.0 letters]; P = .24, respectively), or eyes with intermediate AMD that improved (1.8 letters [2.4 letters]; P = .49 and 1.0 letter [3.9 letters]; P = .80, respectively), nor the nonfoveal GA eyes (0.6 letters [1.4 letters]; P = .67 and 3.6 letters [2.1 letters]; P = .11, respectively; Figure 3). There were also no longitudinal changes in LLD identified for all groups (P ≥ .17).

In examining all eyes with intermediate AMD, there were no relationships identified between baseline LLD and the subsequent change in BCVA, LLVA, or central microperimetric sensitivity over the 12-month period (P ≥ .07; Figure 4).

**Discussion**

Microperimetry has been used previously to examine functional changes in the early stages of AMD at cross section and to monitor disease progression and response to treatments in advanced stages of AMD. However, this is the first study, to our knowledge, that examines whether micro-

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**Table:**

<table>
<thead>
<tr>
<th>Ring No.</th>
<th>Pointwise Sensitivity, Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
</tr>
<tr>
<td>1</td>
<td>26.12 (0.25)</td>
</tr>
<tr>
<td>2</td>
<td>27.07 (0.16)</td>
</tr>
<tr>
<td>3</td>
<td>26.91 (0.13)</td>
</tr>
<tr>
<td>4</td>
<td>26.31 (0.13)</td>
</tr>
</tbody>
</table>

Changes in mean (SE) pointwise sensitivity for eyes with intermediate age-related macular degeneration, graded as having remained stable or progressed at different eccentricities (left).

*Changes at P < .05 compared with the first visit (right).
perimetry is useful for detecting functional changes in the early stages of AMD over a relatively short follow-up period of 12 months.

In this present study, we found that microperimetry was able to detect changes in sensitivity to luminance increments over a 12-month period for eyes that either remained stable or showed disease progression in the early stages of AMD. These changes occurred mainly in the parafoveal region, which previous studies have observed to be the region of predominant photoreceptor loss\textsuperscript{23,24} and dysfunction\textsuperscript{25} in eyes with AMD. Microperimetry was also able to detect an improvement in sensitivity for eyes where the pathological features improved and change was not identified in control eyes, suggesting that the changes observed in the intermediate AMD over this period were not merely a result of time. Although these changes may appear small, on average, they are better appreciated when the total amount of change is considered. For example, a $-0.41$ dB decline in mean PWS over the 12-month period (such as that found in eyes graded as having progressed) represents a total change of $-15$ dB from the 37 points examined in this study; this can be equivalent to having 3 points fall outside our previously reported 95% test-retest limits for PWS of $\pm 4.37$ dB.\textsuperscript{16} Therefore, the ability to detect these changes at a group level over only a 12-month duration of follow-up suggests that microperimetry is worth exploring as a method for assessing the efficacy of interventions over a shorter duration of follow-up than currently required. However, the implications of this short-term functional decline on the development of late-stage disease and vision loss still remain to be determined.

We also included eyes with nonfoveal GA in this study to confirm that microperimetry was able to detect changes in sensitivity over a 6-month period, previously shown in another study using a different microperimeter.\textsuperscript{4} Our results supported the validity of this measure in a more advanced stage of disease. In this study, functional improvement observed following spontaneous drusen regression in some eyes was also in line with previous studies that showed drusen could resolve without leaving any significant pathological
changes. Of interest, these participants with intermediate AMD who exhibited improvement had poorer microperimetric sensitivity at baseline compared with the other participants who remained stable or worsened and we observed that they typically also had a larger baseline drusen load. This is consistent with a previous study that showed spontaneous drusen regression tended to occur in eyes with a larger baseline drusen volume.

It is possible that the longitudinal decline of microperimetric sensitivity observed in participants with intermediate AMD whose pathology remained stable or worsened may be reflected in the changes in structural parameters observed on spectral-domain optical coherence tomography. These parameters included the integrity of the photoreceptor inner segment ellipsoid band and drusen volume that occurred with disease progression in the early stages of AMD, both of which have been reported to correlate strongly with microperimetric sensitivity. Changes in the inner segment ellipsoid band integrity were invisible on CFP and volumetric changes of drusen were not completely captured by subjective side-by-side grading of CFP. Therefore, this may account for the reduction in sensitivity in AMD eyes where the pathological features appeared unchanged on CFP during the period of follow-up. Future studies that correlate these longitudinal changes on microperimetry with changes on high-resolution in vivo imaging may allow structural parameters, such as drusen volume, to be used as biomarkers of disease progression.

Changes in BCVA and LLVA were not identified over the 12-month period, even in eyes with nonfoveal GA that displayed marked reduction in microperimetric sensitivity, confirming previous reports that visual acuity measurements are insufficiently sensitive as a measure in early stages of AMD and are much less sensitive than microperimetry. In addition, although other studies found LLD to be predictive of subsequent vision loss and the rate of enlargement of the atrophic area in eyes with noncentral GA, we did not find LLD to be predictive of subsequent changes in visual acuity measures or central microperimetric sensitivity in eyes with intermediate AMD.

The significant intrasession learning effect found in this study during the first visit but not the 2 subsequent visits also expands on our previous findings in a smaller cohort. This finding was crucial because there would not have been a reduction in microperimetric sensitivity observed in the eyes with intermediate AMD that remained stable or progressed over the 12-month period if the first examination during the first visit was used ($P = .44$; data not shown). This underscores the importance of discarding the first baseline examination for participants who have not previously performed microperimetry, especially in the context of clinical trials and studies, so that changes in visual function can be accurately determined. These findings also suggest that discarding the first examination during subsequent visits is not necessary, although this needs to be confirmed on examinations performed with longer intersession intervals.

Conclusions

Microperimetry detected subtle functional changes, particularly in the parafoveal region over a 12-month period of follow-up in eyes with intermediate AMD when the pathological features either remained stable or progressed, although still remaining within the early stages of AMD. Microperimetry was also able to detect functional changes in eyes where changes were not identified by visual acuity measures in this slow progressive disease.

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