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Structural Changes Associated with Delayed Dark Adaptation in Age-Related Macular Degeneration

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Purpose: To examine the relationship between dark adaptation (DA) and optical coherence tomography (OCT)–based macular morphology in age-related macular degeneration (AMD).

Design: Prospective, cross-sectional study.

Participants: Patients with AMD and a comparison group (>50 years) without any vitreoretinal disease.

Methods: All participants were imaged with spectral-domain OCT and color fundus photographs, and then staged for AMD (Age-related Eye Disease Study system). Both eyes were tested with the AdaptDx (MacuLogix, Middletown, PA) DA extended protocol (20 minutes). A software program was developed to map the DA testing spot (2° circle, 5° superior to the fovea) to the OCT B-scans. Two independent graders evaluated the B-scans within this testing spot, as well as the entire macula, recording the presence of several AMD-associated abnormalities. Multilevel mixed-effects models (accounting for correlated outcomes between 2 eyes) were used for analyses.

Main Outcome Measures: The primary outcome was rod-intercept time (RIT), defined in minutes, as a continuous variable. For subjects unable to reach RIT within the 20 minutes of testing, the value of 20 was assigned.

Results: We included 137 eyes (n = 77 subjects), 72.3% (n = 99 eyes) with AMD and the remainder belonging to the comparison group. Multivariable analysis revealed that even after adjusting for age and AMD stage, the presence of any abnormalities within the DA testing spot (ß = 4.8, $P < 0.001$), as well as any abnormalities in the macula (ß = 2.4, $P = 0.047$), were significantly associated with delayed RITs and therefore impaired DA. In eyes with no structural changes within the DA testing spot (n = 76, 55.5%), the presence of any abnormalities in the remaining macula was still associated with delayed RITs (ß = 2.00, $P = 0.046$). Presence of subretinal drusenoid deposits and ellipsoid zone disruption were a consistent predictor of RIT, whether located within the DA testing spot ($P = 0.001$ for both) or anywhere in the macula ($P < 0.001$ for both). Within the testing spot, the presence of classic drusen or serous pigment epithelium detachment was also significantly associated with impairments in DA ($P \leq 0.018$).

Conclusions: Our results suggest a significant association between macular morphology evaluated by OCT and time to dark-adapt. Subretinal drusenoid deposits and ellipsoid zone changes seem to be strongly associated with impaired dark adaptation. *Ophthalmology 2017;■:1–13 © 2017 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is a multifactorial disease,[1] currently the leading cause of severe vision loss in subjects older than 50 years in developed countries and the third-leading cause worldwide.[2] AMD prevalence is predicted to increase because of the anticipated aging of the global population, so that by 2040, 288 million people are expected to have this disease.[2] Patients present with drusen and pigment changes in the macula in early and intermediate AMD, which may progress to advanced disease manifesting as geographic atrophy (GA) or choroidal neovascularization (CNV) in some cases.[3,4] Visual acuity (VA) loss typically occurs late in the disease course,[5] making VA a less useful measure of retinal function in early and intermediate AMD. Despite its well-recognized limitations in characterizing visual impairment of AMD,[6] VA remains the most widely accepted functional outcome measure for this disease.

Several researchers have tried to establish other functional outcome measurements in AMD, including contrast sensitivity,[7] low-luminance VA, photopic or scotopic light sensitivity,[8,9] and dark adaptation (DA).[5] Patients with AMD often report difficulties performing activities at night, with prior work showing that higher levels of self-reported problems in night vision are associated with an increased risk of vision loss.[10] Moreover, recent studies have shown that DA can differentiate AMD from healthy

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eyes, as well as detecting the different stages of the disease.[5,11,12] Building off this prior work, there is now a commercially available device—the AdaptDx (MacuLogix, Middletown, PA) dark adaptometer—that can be used for testing the time to dark-adapt in patients. Its standard protocol bleaches an area of 2 degrees superior to the central fovea (from now on denoted as DA testing spot) and measures time to dark-adapt with very high sensitivity and specificity.[12]

Most of the published literature about DA in AMD characterized the disease using color fundus photographs (CFP),[5,11,12] as these remain the gold standard for diagnosis and staging.[13] CFPs predominantly use drusen as an index for AMD and have well-recognized limitations.[14] As a noninvasive imaging method capable of resolving cross-sectional anatomy, optical coherence tomography (OCT) offers several important advantages in the assessment of AMD,[15–17] and is currently widely used in daily clinical practice. Importantly, OCT has enabled clinicians and researchers to better identify some lesions, such as subretinal drusenoid deposits,[18] which may have important independent prognostic value.[19]

Little has been published about the relationship between time to dark-adapt and structural OCT changes in AMD.[20–22] Given the growing role of functional measures in AMD, like DA, and the foundational role of OCT in clinical practice, we set out to better define this structure–function relationship of OCT and DA in AMD. In this study, we used spectral-domain OCT (SD OCT) to assess macular morphology in a cohort of AMD and healthy eyes, and evaluated the time to dark-adapt, measured as rod-intercept time (RIT). We then assessed the relationship between DA and type of abnormalities seen in the DA testing spot, as well as within the entire macula.

Methods

This study was developed by the Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, and is part of a prospective, cross-sectional, observational project on AMD biomarkers. It was conducted in accordance with Health Insurance Portability and Accountability Act requirements and the tenets of the Declaration of Helsinki, and was approved by the Massachusetts Eye and Ear Institutional Review Board. All included participants provided written informed consent.

Study Protocol and Procedures

We recruited and consented consecutive patients with a diagnosis of AMD (assessed by a retina specialist) when they came to their regular appointments at our Retina Service. We excluded subjects with any other vitreoretinal disease, active uveitis or ocular infection, significant media opacities that precluded the observation of the ocular fundus, refractive error equal to or greater than 6 diopters of spherical equivalent, formal diagnosis of glaucoma with a cup-to-disc ratio superior to 0.7, history of retinal surgery, history of any ocular surgery or intraocular procedure (such as laser and intraocular injections) within the 90 days before enrollment, and diagnosis of diabetes mellitus, with or without concomitant diabetic retinopathy. Additionally, a comparison group of subjects aged 50 years or older, without any evidence of AMD in both eyes, was included and the same exclusion criteria were applied.

All participants underwent a comprehensive eye examination, including best-corrected VA (for analysis, converted to logMAR), current refraction, intraocular pressure, slit-lamp biomicroscopy, and dilated fundus examination. A standardized questionnaire was designed specifically for this study (including data on demographics, past medical history, and current medications) and applied to all study participants.

The eyes of subjects were also imaged with nonstereoscopic 7-field CFP (Topcon TRC-50DX; Topcon Corporation, Tokyo, Japan) for AMD diagnosis and grading (detailed below), as well as with SD OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). The initial SD OCT imaging protocol was an enhanced-depth imaging (EDI) high-resolution volume centered in the fovea, with 61 lines, 30×25 degrees, 30 frames automatic real time (ART). Due to the burden on patients, this was modified in the course of the study to an EDI high-resolution volume, 97 lines, 20×20 degrees, 15 frames ART. If the referring retina specialist deemed it necessary, fluorescein angiography was performed as part of the regular clinical assessment of patients with CNV.

Finally, subjects underwent DA testing, according to the protocol below. To avoid prior light exposure, DA was performed on a separate day, within a maximum time limit of 1 month after study inclusion.

Dark-Adaptation Testing

A trained optometrist confirmed the current refraction of all participants and optimized it when required. After dilation to ≥6 mm, DA was performed using the AdaptDx dark adaptometer (MacuLogix, Middletown, PA). Corrective lenses were introduced to account for the 30-cm viewing distance. Before the beginning of the actual testing, a 2-minute demonstration test (available in the commercialized software) was performed to familiarize the patient with the AdaptDx procedures. This test is performed in the dark, and it uses a 5 scotopic cd/m^2 bleaching flash, which is the same intensity as the maximum stimulus intensity. When the demonstration test was over, the patients were asked about any questions. If they were clear on the task, the optometrist proceeded to the actual testing—between transitions (from the demonstrating test to the actual test) the room lights were kept off. Both eyes were tested separately (the right eye always first), with a minimum resting period of 15 minutes between them (during testing, the fellow eye was occluded with an eye patch). The extended protocol (20 minutes) was followed.[12] Eyes were bleached by exposure to a 505-nm photoflash (0.8-ms duration, 1.8×10^4 scot cd/m^2 intensity), equivalent to 76% bleaching level for rods. The flash of light passed through a square aperture sized to bleach a 6° area of the retina centered at 5° on the inferior visual meridian. Sensitivity measurements began immediately after bleaching. The subject focused on the fixation light and indicated when a stimulus light was visible by pushing a hand-held button. The stimulus light was a 505-nm, 2° circular test spot, located at 5° on the inferior visual meridian (anatomically, 5° superior to the central fovea) (Fig 1).

Sensitivity was estimated by using a 3-down/1-up modified staircase threshold estimate procedure. The initial stimulus intensity was 5 scot cd/m^2. The stimulus light was presented every 2 or 3 seconds for a 200-ms duration. If the stimulus was detected, the patient was given 2 seconds to respond by pushing a response button. If the subject indicated that the stimulus was visible, the intensity was decreased for each successive presentation in steps of 0.3 log units until the subject stopped responding that the stimulus was visible. If the subject indicated that the stimulus light was not visible, the intensity of the target was increased for each successive presentation in 0.1-log-unit steps until the subject responded that the stimulus light was once again visible. This intensity was defined as a threshold. Successive threshold measurements started with the