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Peripheral Retinal Changes Associated with Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2

*Age-Related Eye Disease Study 2 Report Number 12 by the Age-Related Eye Disease Study 2 Optos PEripheral RetinA (OPERA) Study Research Group**

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Purpose: To compare rates of peripheral retinal changes in Age-Related Eye Disease Study 2 (AREDS2) participants with at least intermediate age-related macular degeneration (AMD) with control subjects without intermediate age-related changes (large drusen).

Design: Cross-sectional evaluation of clinic-based patients enrolled in AREDS2 and a prospective study.

Participants: Participants from prospective studies.

Methods: The 200° pseudocolor and fundus autofluorescence (FAF) images were captured on the Optos 200 Tx Ultrawide-field device (Optos, Dunfermline, Scotland) by centering on the fovea and then steering superiorly and inferiorly. The montaged images were graded at a reading center with the images divided into 3 zones (zone 1 [posterior pole], zone 2 [midperiphery], and zone 3 [far periphery]) to document the presence of peripheral lesions.

Main Outcome Measures: Peripheral retinal lesions: drusen, hypopigmentary/hyperpigmentary changes, reticular pseudodrusen, senile reticular pigmentary changes, cobblestone degeneration, and FAF abnormalities.

Results: A total of 484 (951 eyes) AREDS2 participants with AMD (cases) and 89 (163 eyes) controls without AMD had gradable color and FAF images. In zones 2 and 3, neovascularization and geographic atrophy (GA) were present, ranging from 0.4% to 6% in eyes of cases, respectively, and GA was present in 1% of eyes of controls. Drusen were detected in 97%, 78%, and 64% of eyes of cases and 48%, 21%, and 9% of eyes of controls in zones 2 and 3 superior and 3 inferior, respectively ($P < 0.001$ for all). Peripheral reticular pseudodrusen were seen in 15%. Senile reticular pigmentary change was the predominant peripheral change seen in 48% of cases and 16% of controls in zone 2 ($P < 0.001$). Nonreticular pigment changes were less frequent in the periphery than in the posterior pole (46% vs. 76%) and negligible in controls.

Conclusions: Peripheral retinal changes are more prevalent in eyes with AMD than in control eyes. Drusen are seen in a majority of eyes with AMD in both the mid and far periphery, whereas pigment changes and features of advanced AMD are less frequent. Age-related macular degeneration may be more than a "macular" condition but one that involves the entire retina. Future longitudinal studies of peripheral changes in AMD and their impact on visual function may contribute to understanding AMD pathogenesis. *Ophthalmology 2016;■:1–9 Published by Elsevier on behalf of the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD), a heterogeneous disease with complex genetic associations, is the leading cause of blindness in the developed world.[1] Both pathologic and clinical studies have demonstrated the presence of peripheral retinal changes, including retinal pigmentary changes and drusen in eyes with AMD.[2,3] Some of the lesions of neovascular AMD in a study of autopsy eyes were located not only in the macula but also in the retinal periphery.[2] The clinical significance of such peripheral retinal lesions in AMD is unknown. Until recently, these peripheral retinal changes were difficult to document. However, with the development of the ultrawide-field imaging using the

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Optos 200T× imaging device (Optos, Dunfermline, Scotland), changes in the retinal periphery can be reproducibly imaged. Optos is an scanning laser ophthalmoscopy−based system with an ellipsoidal mirror that permits simultaneous central pole-to-periphery visualization of up to 200° of the retina with or without mydriasis. Color images are captured in pseudocolor using 2-color laser, red (633 nm) and green (532 nm) wavelengths.[4] Fundus autofluorescence (FAF) also can be obtained using the green 532 nm laser for excitation and an emission filter (570−780 nm) to detect the autofluorescence. This technology has been described in previous studies evaluating the retinal periphery of persons with AMD in both a clinic-based study and a population-based study.[5,6]

We conducted an ancillary study of imaging the peripheral retina in persons with at least intermediate AMD enrolled in the Age-Related Eye Disease Study 2 (AREDS2) and controls from 2 AREDS2 clinical sites (Duke University and the National Eye Institute). The purpose of this ancillary study was to examine the frequency of peripheral retinal alterations and to compare with controls to determine whether these peripheral changes were due mostly to aging rather than AMD.

Methods

Study Population

The study design for AREDS2 is described in detail in a previous report but briefly summarized in the current article (AREDS2, ClinicalTrials.gov identifier NCT00345176).[7] Between 2006 and 2008, 4203 participants ranging from 50 to 85 years of age were enrolled at 82 retinal specialty clinics in the United States. At enrollment, participants were included if they had bilateral large drusen or unilateral advanced AMD in 1 eye and large drusen in the fellow eye. The AREDS2 participants were randomly assigned to placebo, lutein/zeaxanthin, docosahexaenoic acid plus eicosapentaenoic acid, or the combination. Although baseline and annual conventional 45° stereoscopic fundus photographs were obtained by certified photographers, we obtained at AREDS2 close-out study visits (2011−2012) additional fundus photographs using the Optos ultrawide-field imaging up to 200° in 17 AREDS2 clinics. In 2 of these AREDS2 clinics, additional studies of AMD were conducted and the participants provided the controls for this study. The controls with no evidence of posterior AMD were enrolled in another ancillary AREDS2 study of prospective spectral domain-optical coherence tomography imaging, which was conducted to evaluate the correlation of optical coherence tomography changes with progression of AMD detected on color fundus photographs and FAF (A2A SDOCT Study, ClinicalTrials.gov identifier NCT00734487). A study of dark adaptation using the AdaptRx dark adaptometer (MacuLogix, Atlanta, GA) in persons with varying degrees of AMD also recruited controls without posterior changes of AMD. Controls from these 2 studies were imaged with the Optos device.

This AREDS2 OPTOS PEripheral RetinA (OPERA) Study was reviewed and approved by each of the institutional review boards, and written informed consent was obtained from all participants. The research was conducted according to the tenets of the Declaration of Helsinki.

Imaging Protocol

All photographers, who were certified by Optos personnel for acquiring images according to a standardized protocol, obtained 200° images that were first centered at the fovea (on axis) and then steered superiorly and inferiorly, using the fixation light within the equipment to guide the steering. These 3 images were then montaged into 1 single image (Fig 1). This protocol was used for acquiring both the color fundus photographs and the FAF images.

Grading Protocol

All images were assessed by trained graders using a standardized protocol at the University of Wisconsin Fundus Photograph Reading Center. A circular grid with 3 concentric circles was placed centered at a midpoint between the temporal edge of the optic nerve and center of fovea (Fig 1). The grid contains 3 zones and is adapted from the Study of Ocular Complication of AIDS, which assessed cytomegalovirus retinitis in the retinal periphery.[8] Zone 1 has a radius of approximately 5.4 mm (3 disc diameters) and roughly corresponds to the posterior pole. Zone 2 extends from the edge of zone 1 anteriorly with a radius of 16.2 mm (9 disc diameters) and overlaps the vortex veins. Zone 3 is the region anterior to zone 2. Zones 1 and 2 are divided into 4 quadrants: superonasal, superotemporal, inferonasal, and inferotemporal. Zone 3 is divided into superior and inferior hemispheres. A properly aligned grid fulfills 2 criteria: The center point of zone 1 corresponds to the center of the line that connects the disc and macula; the outer circle dividing zone 2 and zone 3 crosses the vortex veins at approximately 3 or more vascular landmarks. Both mounting of the grid and viewing of images were performed in proprietary software provided by Optos (V2vantage Software).

The ability to grade was assessed for the entire image initially and then for each zone separately. For the entire image to be considered gradable, the grid had to be properly aligned. A montage was considered to be the best quality if both zones 1 and 2 were gradable in all quadrants, borderline quality if 1 or more quadrants in zones 1 and 2 were ungradable, and poor quality if all subfields in both zones 1 and 2 were ungradable. For a subfield with a zone to be considered gradable, at least 50% of the subfield had to be visible.

Similar to standard color photographic grading for AREDS2, the grader first evaluated neovascular AMD characteristics.[9] Presence of neovascular AMD was assessed in zone 1 as a whole and for each quadrant in zone 2 and each hemisphere in zone 3. Definite presence is documented when at least 2 of the 5 features are consistent with neovascular AMD (subretinal fluid, intraretinal, subretinal, or subretinal pigment epithelium blood associated with neovascular AMD, intraretinal lipid exudates, subretinal fibrin or fibrosis, and fibrovascular or serous pigment epithelial detachment). The presence of a disciform scar by itself was considered definite neovascular AMD.

Presence of drusen, increased pigment, decreased pigment, and geographic atrophy (GA) was evaluated in each quadrant of zones 1 and 2 and each hemisphere of zone 3. Detailed assessment of drusen included a categoric count of large drusen in each subfield as 1 to 5, 6 to 20, or >20. Presence and percentage involvement of a subfield with reticular pseudodrusen were graded as <25%, 25% to 49%, 50% to 74%, and ≥75%. Peripheral abnormalities are evaluated in each subfield of zone 2 and each hemisphere of zone 3 and include reticular pigment changes, lattice, and cobblestone degeneration.

Autofluorescence montages were overlaid with a grid and assessed for image quality similar to color photographs. Both color and autofluorescence images were evaluated together by the same grader. Presence of hypoautofluorescence and hyperautofluorescence adjacent to hypoautofluorescence (halo) was graded. Any other area of hyperautofluorescence greater than drusen circle C2 (>250 μ) was noted. Presence of reticular pseudodrusen from autofluorescence images and percentage involvement of a subfield were graded as <25%, 25% to 49%, 50% to 74%, and ≥75%. Peripheral