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Polarization Variability in Age-related Macular Degeneration

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Abstract

Significance—Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss. Complementary imaging techniques can be used to better characterize and quantify pathological changes associated with AMD. By assessing specific light/tissue interactions, polarization sensitive imaging can be used to detect tissue disruption early in the disease process.

Purpose—To compare variability in central macular polarization properties in patients with non-exudative age-related macular degeneration (AMD) and age-matched controls.

Methods—A scanning laser polarimeter (GDx, LDT/CZM) was used to acquire 15×15 degree macular images in 10 subjects diagnosed with non-exudative AMD and 10 age-matched controls. The coefficient of variation (COV, standard deviation/mean) was used to quantify variability in pixel intensity in the central 3.3 degrees of the macula for custom images emphasizing multiply scattered light (the Depolarized Light Image) and polarization retaining light (the Maximum of the Parallel Detector Image). The intensity COV was compared across subject categories using paired t-tests for each image type.

Results—The COV in the central macula was significantly higher in the AMD subject group (average 0.221, 95% CI 0.157 to 0.265) when compared to matched controls (average 0.120, 95% CI 0.107 to 0.133) in the Depolarized Light Image ($p = 0.01$). The COV in the Maximum of the

Parallel Detector Image was not statistically different between the two subject groups (AMD average 0.162, 95% CI 0.138 to 0.185; Control average 0.137, 95% CI 0.115 to 0.158, $p = 0.213$).

Conclusions—Variability in multiply scattered light is higher than that of light that is more polarization preserving in patients with non-exudative AMD. Multiple scattering may act as an early indicator representing disruption to the macula in early AMD.

Keywords

age-related macular degeneration; retina; polarimetry; depolarization; spectral domain optical coherence tomography

The central macula is a well-ordered network of interconnected cells and prone to damage in a number of sight threatening retinal diseases, including age-related macular degeneration. The pathological features associated with age-related macular degeneration are characterized using traditional clinical techniques, which include clinical fundus examination and fundus photography. Classification schemes based on fundus appearance as seen with spectrally broadband, referred to as “white,” flood illumination sources are well established and have been incorporated into major longitudinal studies and clinical trials for decades. With regard to age-related macular degeneration, one of the most recognized predictors of progression is the fundus photograph-based Age-Related Eye Disease Study classification system.¹ The use of visible light to examine the retina presents some limitations, particularly when examining the aging eye, where increased scatter is common and degrades image quality. Despite the widespread use of broadband flood illumination sources, clinical examination and fundus photography may underestimate the true extent of retinal pathology associated with age-related macular degeneration seen in newer imaging techniques, including spectral domain optical coherence tomography.² Separating the color channels from fundus photographs has the potential to enhance the visibility of some pathological features, but those features are often detected through the blue wavelength channel, the wavelength range most prone to scatter from media opacifications, underestimating the extent of age-related macular degeneration pathology relative to spectral domain optical coherence tomography.³

Histological studies demonstrate that pathology associated with age-related macular degeneration is far more widespread than can be determined using traditional imaging techniques, and the pathology itself is much more diverse, including basal laminar deposits, basal linear deposits, drusen of varying internal densities, and disruption to melanin distribution,^{4–6} encompassing the entire macular region by the time pathological changes are clinically detectable. Near infrared *en face* imaging has the potential to overcome some limitations of more traditional techniques, as it more easily penetrates scattering features like nuclear sclerotic lens changes.⁷ Confocal scanning laser ophthalmoscopy can be used to acquire good quality images with high contrast through relatively small pupil sizes, greatly reducing the need for pupil dilation in most individuals for the purposes of assessing the central macula. Age-related macular degeneration specific changes are easily delineated using near infrared imaging in both direct modes^{7–14} and indirect modes.^{8,15} Features like drusen, pigment clumping, and neovascularization have all been assessed and systematically characterized using near infrared *en face* imaging, but not incorporated into major

longitudinal studies, which continue to rely on pathological classification primarily from fundus photography.

Scanning laser polarimetry incorporates multiple polarization conditions into confocal imaging to enhance visibility of specific features in the normal and diseased retina. Scanning laser polarimetry imaging has been used to differentiate normal features from pathologic changes including drusen,¹⁶ pigment clumping,¹⁷ and exudative age-related macular degeneration changes,^{18,19} correlating with visual function.²⁰ From the same raw dataset, scanning laser polarimetry imaging can be used to isolate and quantify changes to the photoreceptor axons in the central macula, the Henle fiber layer,^{21–24} based on inherent birefringent properties and isolate light returning from the retinal pigment epithelium based on the depolarizing properties of the melanin and melanosomes.²⁵ The shadowing effect of the blood vessels from the depolarizing light returning from the retinal pigment epithelium also enhances the contrast of the retinal vasculature.²⁶ With the exception of the retinal vasculature, light depolarization from the retinal pigment epithelium monolayer remains relatively uniform across the posterior pole in the normal, healthy eye. The difference between polarization retaining and depolarizing structures has the potential to provide some insight into the nature of pathological changes in the earliest stages of age-related macular degeneration based on predictable light/tissue interactions known to occur at the Bruch's membrane/retinal pigment epithelium interface.^{16,17} Irregularity of the retinal pigment epithelium cells or their components produce local variability in depolarization, which can be used to assess the regularity and structural integrity of the retinal pigment epithelium independent of other retinal cells/structures. As the retinal pigment epithelium becomes disrupted, even in early age-related macular degeneration, non-uniformity of the retinal pigment epithelium cells or their contents should manifest as intensity changes in images that emphasize light depolarization. This image intensity variability can be quantified using metrics like the coefficient of variation, the standard deviation normalized by the average.

Despite the benefits of detecting intrinsic light tissue interactions, as an *en face* imaging technique scanning laser polarimetry remains limited in its ability to localize features axially in the retina with a moderate depth of field relative to more highly magnified imaging techniques. Other complementary techniques, including spectral domain optical coherence tomography, provide cross sectional imaging of the retina with good axial and lateral resolution, which could be used as a complementary technique that provides information about the relative depths of retinal features. Spectral domain optical coherence tomography instruments that combine imaging modalities can be used to capture *en face* images and registered cross sectional images simultaneously, allowing for co-localization of features in the retina. This capability has helped improve identification, quantitative assessments, and understanding of retinal pathology associated with age-related macular degeneration. Through the collection of closely spaced cross sectional images, optical coherence tomography can be used to generate three-dimensional representations of the retina, which can be used to measure drusen volume, internal consistency, and lateral extent^{3,27–30} Because of the resolution properties of optical coherence tomography, and ability to show diverse changes more closely resembling histology, optical coherence tomography is frequently used to differentiate changes seen in *en face* imaging. In recent years, spectral

domain optical coherence tomography has been widely adopted clinically and incorporated into major longitudinal studies, including Age-Related Eye Disease Study 2.

In this study we compared the variability in light depolarization in the central macula between patients with non-exudative age-related macular degeneration and matched controls by using a standardized metric of variability, the coefficient of variation. Because of the nature of the specific light tissue interactions, we hypothesize that variability in depolarized light should differ from light that is directly backscattered, which can be acquired from the same dataset. We also characterized pathological features associated with non-exudative age-related macular degeneration, and hypothesized that alterations to the depolarized and directly backscattered light would provide some insight into the exact nature of features characteristic of age-related macular degeneration.

METHODS

Subjects

We randomly selected and imaged one eye in 10 non-exudative age-related macular degeneration patients (6 females, 4 males, age range 56 to 81 years old) and one eye in 10 clinically normal age-matched patients (7 females, 3 males, age range 59 to 81 years old). All subjects in both groups were required to have undergone a comprehensive eye examination within the past year. Subjects in the age-related macular degeneration group were required to have evidence of pathological features characteristic of non-exudative age-related macular degeneration with relatively good visual acuity, ranging from 20/20 to 20/40 in the tested eye. Subjects in the control group were required to have normal ocular findings with visual acuity 20/20 or better, unless reduced visual acuity could be attributed to normal lens opacification, assessed through clinical evaluation. One of the control subjects had visual acuity of 20/25, with the remaining having 20/20 acuity. Patients with systemic diseases that carry a high likelihood of ocular manifestations were excluded from both groups.

Age-related macular degeneration and control subjects were recruited from the Indiana University School of Optometry (Bloomington, IN, USA), following the approved human subjects protocol procedures. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study. The research followed the tenets of the Declaration of Helsinki.

Instrumentation

Each subject was imaged using a confocal scanning laser polarimeter (GDx, LaserDiagnostic Technologies/Carl Zeiss Meditec, Dublin, CA). The GDx uses a 780 nm linearly polarized light source to scan a raster on the retina and has two detectors, a parallel detector collecting light with the same polarization as the input light; and a crossed detector, collecting light with polarization that is 90° from the input polarization. Each of the 2 detectors produces images at 20 different input polarizations, for a total of 40 images per raw dataset. 15 × 15° macula centered images were acquired with an acquisition time of ~ 0.9 seconds. Each image has 256 × 256 pixel resolution with 8-bit grayscale. The resolution

of the GDx is nominally 18 μm , limited by the digital resolution, with an optical resolution of approximately 7 μm . The instrument used for this study has a fixed birefringent element with a magnitude of 60 nm (singlepass retardance) and a fast axis oriented at 15° nasally downward. The polarization element in this specific instrument is designed to compensate for corneal birefringence,³¹ but corneal compensation is incomplete in most individuals.³² Incomplete corneal compensation results in a macular cross pattern, which can be used to localize the fovea in normal subjects²² and subjects with retinal pathology associated with age-related macular degeneration but some remaining cone axons.²⁴

To describe our scanning laser polarimetry findings in clinically relevant terms, 9 subjects were imaged using a Spectralis spectral domain optical coherence tomographer (Heidelberg Engineering, Carlsbad, CA). We found that the duration needed to acquire high density b-scans for averaging could be time intensive and difficult for patients with moderate fixation. As a compromise, we used 60 μm nominal spacing between b-scans, which provides at least one good sample for drusen 63 μm in diameter, the definition of small drusen in many age-related macular degeneration grading protocols.³³ Individual horizontal b-scans, were acquired from inferior to superior retina (y dimension) over a 20° horizontal x 15° vertical area, centered on the central macula. To reduce noise, each b-scan used for comparison was the average of 16 individual registered b-scans. Corresponding scanning laser ophthalmoscope images were acquired simultaneously allowing for co-alignment of the spectral domain optical coherence tomography b-scan images with the scanning laser ophthalmoscope images. The central imaging wavelength for the Heidelberg Spectralis spectral domain optical coherence tomography is 870 nm. Images were acquired in high resolution mode with an axial resolution of 7 μm , a lateral resolution of 14 μm , and a-scan density of 1024 a-scans/b-scan. The resolution of the corresponding scanning laser ophthalmoscope images in high resolution mode are nominally 6 μm .

A subset of 4 subjects with specific pathological features characteristic of age-related macular degeneration also underwent fundus photography, providing examples of features commonly seen on clinical examination and representative of our study population. For fundus photography, pupils were dilated with a combination of 1% Tropicamide and 2.5% Phenylephrine. 35° macula-centered fundus photographs were acquired using a Topcon TRC-50DX fundus camera (Topcon, Oakland, New Jersey).

Scanning Laser Polarimetry Image Processing

Raw image data from the GDx were processed using custom Matlab routines (Matlab, Mathworks, Natick, MA), with three image types used for this study. These images differ based on polarization content for each pixel over the 20 input polarizations and emphasize different retinal structures resulting from light/tissue interactions.^{16–24} The images used for this study were the Maximum Phase of the Crossed Detector Image, the Maximum of the Parallel Detector Image and the Depolarized Light Image (Figures 1A, 1B, and 1C respectively), described previously.^{16–24, 34,35} The Maximum Phase of the Crossed Detector Image is a pseudocolor image that is computed as the amplitude of the modulation across polarization input angles, but only for light returning to the crossed detector. This computation demonstrates the combined phase retardation at each pixel due to the

interaction of the birefringent cornea and the cone photoreceptor axons of the Henle fiber layer. The pseudocolor information is used to visualize the polarization input condition that produced the maximum light return to the crossed detector at each pixel. This produces a radially symmetric pattern that was used to precisely position the macula-centered region of interest used for this study. The Depolarized Light Image is computed as the minimum value of the modulated light returning to the crossed detector at each pixel location. This image type emphasizes features that multiply scatter light, while minimizing features that specularly reflect, or singly scatter. The Maximum of the Parallel Detector Image is computed as the maximum value of light returning to the parallel detector at each pixel location. In contrast to the Depolarized Light Image, the Maximum of the Parallel Detector Image emphasizes specularly reflecting or polarization retaining features, which are often located in the more superficial retina. All three scanning laser polarimetry-derived image types are computed from the same raw data set, so retinal locations on each image type from the same data set are corresponding.

For each subject, the center of the macula was determined using the radially symmetric macular cross pattern from the Maximum Phase of the Crossed Detector Image. A region of interest centered on the macula 3.3 degrees in diameter, approximating the area of the innermost Early Treatment Diabetic Retinopathy Study circle, was used and the coefficient of variation (standard deviation/mean) of the pixel intensities within that region of interest was calculated for each subject in the Depolarized Light Image and the Maximum of the Parallel Detector Image. There is an inherent central reflection artifact in GDx images. Prior to data analysis, this artifact was manually removed and replaced column-by-column with the average of the first pixel above and the first pixel below the reflection artifact.²³

Polarization Sensitive vs. Non-Polarization Sensitive Imaging

To demonstrate that pathological features were specific to the Depolarized Light Image of the GDx, and assess whether polarization properties were advantageous in detecting early pathological changes in age-related macular degeneration, we collected scanning laser ophthalmoscope images in 9 of the 10 age-related macular degeneration subjects with the Heidelberg Spectralis. Scanning laser ophthalmoscope images were limited by digital resolution with a nominal resolution of 17 microns per pixel. We calculated the coefficient of variation from pixel intensities in the scanning laser ophthalmoscope images over the same 3.3 degree region of interest for direct comparisons with the GDx. Prior to data analysis, reflection artifacts inherent in the Spectralis scanning laser ophthalmoscope images were manually removed and replaced column-by-column with the average of the first pixel above and the first pixel below the reflection artifact.

Statistical Analysis

The coefficient of variation of the pixel intensity in the macular region of interest was compared across subject categories and instruments using paired t-tests: the coefficient of variation in the Depolarized Light Image in the age-related macular degeneration subjects vs controls; and the coefficient of variation in the Maximum of the Parallel Detector Image in the age-related macular degeneration subjects vs controls. In a subset of 9 subjects with age-related macular degeneration, we also compared the coefficient of variation in the Spectralis

scanning laser ophthalmoscope image vs the Depolarized Light Image; and the Spectralis scanning laser ophthalmoscope image vs the Maximum of the Parallel Detector Image. To account for multiple comparisons, a Bonferroni correction was applied to the resulting p-values.

Co-localization of Pathology in Spectral Domain Optical Coherence Tomography and Scanning Laser Polarimetry Images

To investigate the source of polarization light/tissue interactions resulting from pathological features associated with age-related macular degeneration, images were aligned using the retinal vasculature as landmarks and structures were co-localized across the different imaging modalities. Features of interest included early retinal pigment epithelium irregularities, drusen, subretinal deposits, pigment clumping, hyper-reflective foci overlying drusen, and discontinuity of the photoreceptor inner segment/outer segment junction. The corresponding scanning laser ophthalmoscope images included from the Heidelberg Spectralis indicate the retinal location of b-scan acquisitions and were used to localize specific pathological features in an *en face* representation. The vasculature of the scanning laser polarimetry-derived and scanning laser ophthalmoscope images were aligned in Adobe Photoshop (Adobe, San Jose, California). After alignment, scanning laser ophthalmoscope images and the corresponding spectral domain optical coherence tomography b-scans were cropped to the same dimensions as the scanning laser polarimetry-derived images to allow for direct comparisons across imaging modalities.

RESULTS

Coefficient of Variation in the Depolarized Light Image and the Maximum of the Parallel Detector Image

Figure 2 demonstrates differences between the Depolarized Light Image and the Maximum of the Parallel Detector Image in a control subject (Figure 2A and 2B), compared to a subject with non-exudative age-related macular degeneration (2C, and 2D). The coefficient of variation in the central macula of these subjects (Figure 3) was significantly higher in the macular region of interest in the age-related macular degeneration subject group (average 0.221, 95% confidence interval 0.157 to 0.265) when compared to matched controls (average 0.120, 95% confidence interval 0.107 to 0.133) in the Depolarized Light Image ($p = 0.01$). The coefficient of variation in the Maximum of the Parallel Detector Image was not statistically different between the two subject groups ($p = 0.213$), with an average in the age-related macular degeneration group of 0.162 (95% confidence interval 0.138 to 0.185) and an average in the control group of 0.137 (95% confidence interval 0.115 to 0.158).

Coefficient of Variation in Polarization Sensitive vs. Non-Polarization Sensitive Images

In our sub-analysis of 9 of the 10 age-related macular degeneration subjects, with both Spectralis scanning laser ophthalmoscope and GDx scanning laser polarimetry imaging, the average coefficient of variation was 0.212 (95% confidence interval 0.151 to 0.272) in the Depolarized Light Image, 0.155 (95% confidence interval 0.133 to 0.176) in the Maximum of the Parallel Detector Image, and 0.113 (95% confidence interval 0.09 to 0.135) in the Spectralis scanning laser ophthalmoscope image. There was a significantly lower coefficient

of variation in the Spectralis scanning laser ophthalmoscope image when compared to the Depolarized Light Image ($p<0.01$) and the Maximum of the Parallel Detector Image ($p=0.01$).

Pathology Localization

We found that pathological changes in age-related macular degeneration led to three types of light-tissue changes. First, there is a thickening of structures such as drusen and an elevation of overlying materials, which leads to optical changes, particularly at borders between sloped and flat tissues. Second, there is dense packing vs. amorphous distribution of materials such as lipoproteins that can provide a strong index of refraction change between two types of materials, and even reduce the amount of light that can directly penetrate the fundus at that location. Both of these types of change are often seen on spectral domain optical coherence tomography. Third, there are scattering and polarization changes from disrupted tissues that occur within a layer and are not necessarily thick enough to alter the layer structure on optical coherence tomography. These changes do not necessarily produce a strong index of refraction difference relative to the immediately surrounding tissue, which is needed to produce sufficient interference for visualization in optical coherence tomography. These changes are frequently better visualized by polarization changes that are not used in conventional optical coherence tomography imaging and better visualized by multiply scattered light that is directed laterally across the retina before returning to the imaging system detector.¹⁶ The following cases demonstrate the comparison for selected features in non-exudative age-related macular degeneration for spectral domain optical coherence tomography to 2 different image types in scanning laser polarimetry, to show the complementary nature of these modes of imaging.

Early Retinal Pigment Epithelium Changes—Changes to the regularity of the retinal pigment epithelium could be seen in all imaging modalities (Figure 4); however the contrast and visibility of these features differed across image types. Disruptions to the retinal pigment epithelium appear as small areas of low contrast changes against a reddish orange background in the fundus photograph (Figure 4A), and are difficult to differentiate from other pathological features associated with age-related macular degeneration due to the low contrast and lack of depth information. These changes, correspond with irregularities in the deep retinal layers seen on spectral domain optical coherence tomography (Figures 4B and 4C), which are visible, but subtle alterations in elevation and continuity to the retinal pigment epithelium, affecting the photoreceptor inner segment/outer segment junction in some locations. In scanning laser polarimetry-derived images, the appearance of these early retinal pigment epithelium changes differs based on the type of light/tissue interaction emphasized. Retinal pigment epithelium disruptions are seen as adjacent areas of high and low intensity changes in the Depolarized Light Image (Figure 4D). While still visible in the Maximum of the Parallel Detector Image (Figure 4E), these locations are seen with lower contrast. The low intensity in the Maximum of the Parallel Detector Image demonstrates low reflectivity of these pathological features relative to the surrounding tissue when imaged with near infrared.

Drusen—There is variability in the appearance and contrast of drusen (Figures 5 and 6) on fundus photography (Figure 5A) and on clinical examination. As with disruption to the retinal pigment epithelium, these low contrast structures are frequently difficult to detect against the adjacent fundus background (Figures 5A, 5B, and 6A). One major advantage of spectral domain optical coherence tomography is that drusen are readily seen and can be easily segmented and differentiated based on their morphological characteristics. We found that locations of drusen localized using spectral domain optical coherence tomography (Figures 5C and 6B), and their structural complexity matched features in the Depolarized Light Image (Figure 5D). Small focal drusen with low internal reflectivity appear in the Depolarized Light Image (Figures 5D and 6C) as localized areas with bright depolarizing borders surrounding a low intensity central core (Figures 5D and 6C). Similar to smaller focal drusen, coalesced drusen with low internal reflectivity on spectral domain optical coherence tomography are defined in the Depolarized Light Image by a highly depolarizing border and lower depolarizing central core. When the same regions of interest are aligned in the different imaging modalities, the border of drusen in the Depolarized Light Image matches the boundary of deep retinal elevations detectable in spectral domain optical coherence tomography. In the Maximum of the Parallel Detector Image, we found a range of reflectivity changes associated with drusen that have low internal reflectivity on spectral domain optical coherence tomography. In some instances we found larger areas of low reflectivity in the Maximum of the Parallel Detector Image (Figure 6D), some of which extended beyond the drusen border seen in the Depolarized Light Image (Figure 6C). In other instances, we found low contrast changes (Figure 7A), the boundaries of which corresponded more closely with changes in the spectral domain optical coherence tomography b-scans (Figure 7B) and the Depolarized Light Image (Figure 7C). We also found a subset of drusen with high reflectivity matching changes in the spectral domain optical coherence tomography b-scans and Depolarized Light Images (Figure 7B and 7C). These changes corresponded to locations of increases in reflectivity at the inner segment/outer segment junction or intraretinal hyper-reflective foci overlying photoreceptors (see below) anterior to the photoreceptors in spectral domain optical coherence tomography.

Subretinal Deposits—Subretinal deposits are identifiable and easily distinguished from drusen in spectral domain optical coherence tomography imaging (Figure 8). These deposits appear as hyper-reflective accumulations of material anterior to the retinal pigment epithelium, separating it from the overlying photoreceptors. We found subretinal deposits to be high intensity structures centrally, with a lower intensity surround in the Depolarized Light Image (Figure 8C). This appearance in our population made them distinguishable from drusen. Intensity changes in the Depolarized Light Image match the highly reflective changes separating the retinal pigment epithelium from the photoreceptors in spectral domain optical coherence tomography imaging (Figure 8B). The extent of subretinal deposits were not defined in the Maximum of the Parallel Detector Image with as high contrast (Figure 8D), and appeared as more uniform in intensity.

Pigment Clumping—Pigment clumping, a risk factor indicating poor prognosis in patients with non-exudative age-related macular degeneration,³⁶ is easily identifiable in fundus photographs (Figure 9A), and seen as areas of increased retinal pigment epithelium

thickness and irregularity in the corresponding spectral domain optical coherence tomography b-scans (Figures 9B, 9C). The Depolarized Light Image (Figure 9D) delineates areas of pigment clumping by the high intensity return, consistent with previous findings of pigmentary changes adjacent to the optic disc in glaucoma patients.¹⁷ These locations matched disruption to the deep retina, evident in spectral domain optical coherence tomography imaging (Figure 9C). The lateral extent of pigment clumping is difficult to determine in the spectral domain optical coherence tomography b-scans, but more defined in the Depolarized Light Image.

As with subretinal deposits, the Depolarized Light Image can be used to differentiate pigment clumping from drusen. Pigment clumping changes found in our subjects appeared as a uniform, high intensity structure, unlike drusen, where only the borders appear with high intensity. In comparison to the Depolarized Light Image, the reflectivity changes in the Maximum of the Parallel Detector Image result in lower contrast at the border of pigment clumping (Figure 9E), resulting in poorer differentiation between pigment clumping and drusen, based on more specularly reflected light return.

Hyper-reflective Foci Overlying Photoreceptors—Hyper-reflective foci anterior to the photoreceptor inner segment/outer segment boundary (Figure 7) is commonly found in patients with age-related macular degeneration. These features are easily recognizable in spectral domain optical coherence tomography images (Figure 7B), and appear with high contrast in both scanning laser polarimetry-derived images (Figure 7C and 7D). Unlike retinal pigment epithelium alterations confined to the deeper retinal structures, seen with higher contrast in the Depolarized Light Image, areas corresponding to hyper-reflective foci located more anteriorly are seen as high intensity features in both the Depolarized Light Image (Figure 7C) and the Maximum of the Parallel Detector Image (Figure 7D).

DISCUSSION

In this study we quantified variability in polarization changes in the retina and compared those changes between normal subjects and subjects with non-exudative age-related macular degeneration. We concentrated on two fundamentally different light tissue interactions, 1) depolarized light and 2) light that is primarily specularly reflected. Light in the Depolarized Light Image originates from the scattering properties of the melanin and melanosomes within the retinal pigment epithelium, and irregularly disrupted retinal tissues, while light that is represented in the Maximum of the Parallel Detector Image is predominantly directly backscattered from highly reflective interfaces. When comparing light tissue interactions between non-exudative age-related macular degeneration patients and clinically normal controls, we found higher spatial variability in depolarized light return in the age-related macular degeneration population. Variability in the Maximum of the Parallel Detector Image did not differ significantly between the two groups.

In healthy subjects, the distribution of the retinal pigment epithelium contents is relatively uniform resulting in an even intensity in the Depolarized Light Image across the macula, common in younger normal subjects. The retinal pigment epithelium cells and contents become increasingly disrupted and irregular as a result of normal aging, with disruption

becoming even more pronounced in age-related macular degeneration.^{4,6} Because age-related macular degeneration pathology initially occurs at the retinal pigment epithelium/Bruch's membrane interface, the detection of depolarized light changes may act as a useful optical signature, capable of indicating alterations within the retinal pigment epithelium/Bruch's membrane complex at different stages in the disease process. As the retinal pigment epithelium cells and contents become irregular, the disruption manifests as higher variability in the intensity of the Depolarized Light Image. Here, we show that the coefficient of variation in the intensity of the Depolarized Light Image acts as a more definitive quantitative metric differentiating age-related macular degeneration from controls than near infrared light that is directly backscattered.

Techniques traditionally used to systematically assess changes associated with age-related macular degeneration are often unable to capture the full extent of pathology, and scanning laser polarimetry is a potential complementary tool. Fundus photographs, a clinical standard used in previous major longitudinal studies, suffer reduced contrast and poor image quality due to scattering from the aging media, leaving a large proportion of photographs ungradeable.³⁶ Newer segmentation of the color planes in fundus photographs provides improved contrast of pathological features associated with age-related macular degeneration, but the primary limitation to fundus photography is increased scatter from the more anterior structures, which is exacerbated at shorter wavelengths. Emphasizing short wavelength return in age-related macular degeneration may be useful in delineating some features, but continues to detect fewer pathological features than spectral domain optical coherence tomography.³ The use of near infrared in scanning laser polarimetry imaging has advantages when evaluating optical signatures of retinal disease, as it allows examination of the structural integrity of the retinal pigment epithelium in the central macula through aging media and without attenuation from the overlying macular pigment, which has a peak absorption at much shorter wavelengths. Although variability in short wavelength fundus autofluorescence has been shown to correlate with visual function changes in diseases like central serous chorioretinopathy,³⁷ absorption of the macular pigment becomes problematic, limiting visualization of the deeper retina in the central macula.³⁹ Recent advances in spectral domain optical coherence tomography technology have made it possible to better assess retinal changes associated with age-related macular degeneration, producing more densely spaced cross sectional images which can be used to quantify both drusen area and volume.² Spectral domain optical coherence tomography has been used to characterize the structural composition of drusen, demonstrating that drusen are a much more diverse pathological entity than previously recognized by traditional clinical techniques.³⁹⁻⁴² This diversity of structures, clinically identified collectively as drusen, is consistent with histological findings.⁴³ Our scanning laser polarimetry findings show similar diversity and demonstrate an ability to separate pathological features based on their relative light return to the two detectors collecting differing polarization content.

Even with its better axial resolution, spectral domain optical coherence tomography may be unable to detect some pathological changes associated with age-related macular degeneration. Evidence supporting an underestimation of age-related macular degeneration pathology includes longitudinal studies that demonstrate the apparent regression of age-related macular degeneration pathology over the course of months. These features have been

studied in fundus photography, where regressed pathology cannot be differentiated clinically from normal retinal tissue or pathological changes such as coalesced drusen or atrophic tissues of low contrast.⁴⁴ Similar occurrences have been documented in spectral domain optical coherence tomography, where residual effects of regressed pathology often appear normal, leaving no clinical evidence of their previous existence.⁴² The idea that these areas of pathology truly regress and return to normal structure and function is not supported by histological evidence, which shows nearly complete involvement of the posterior pole in age-related macular degeneration patients. Despite normal appearance on spectral domain optical coherence tomography, locations of regressed pathology are often harbingers for the most advanced age-related macular degeneration changes, including exudation and geographic atrophy.⁴² This suggests that locations with a clinically normal appearance on spectral domain optical coherence tomography may contain degenerative changes that are precursors to advanced age-related macular degeneration, and detection by spectral domain optical coherence tomography may be incidental and timing-dependent in some cases.

While there is no single imaging modality that can capture the entire spectrum of pathological features associated with age-related macular degeneration, scanning laser polarimetry imaging does provide several advantages as a complementary technique. In the scanning laser polarimetry-derived images used in this study, we are able to collect a 15×15 degree dataset that include a diverse number of polarization conditions in under 1 second. The short acquisition time minimizes the effects of poor fixation and eliminates the need for retinal tracking and continued re-alignment of the imaging system to compensate for eye movements. Features that exhibit different light/tissue interactions can easily be co-localized and compared when they are extracted from the same scanning laser polarimetry dataset, which has been used to demonstrate alterations to the deeper retinal architecture with high contrast in central serous chorioretinopathy,³⁴ glaucoma,¹⁷ early age-related macular degeneration,¹⁶ and exudative age-related macular degeneration.^{18–20}

While many of the pathological features we encountered in scanning laser polarimetry imaging had corresponding features in the spectral domain optical coherence tomography b-scans, some did not show alterations on spectral domain optical coherence tomography imaging. One limitation is that our direct comparisons are limited by the sampling density that we chose in our spectral domain optical coherence tomography imaging. This under sampling may cause small drusen and focal pigmentary changes to be missed on spectral domain optical coherence tomography. Additionally, the scan lines depicted in the scanning laser ophthalmoscope image on the Spectralis may lack precise correspondence to cross sectional optical coherence tomography images.⁴⁵ This is shown in the vessel shadowing distribution between the scanning laser ophthalmoscope and optical coherence tomography images in Figure 4B and C. A reasonably high sampling density and assessing features large enough to be detectable in adjacent scan lines, help mitigate this limitation. Despite these limitations, we found spectral domain optical coherence tomography and scanning laser polarimetry to provide useful complementary information, which did not always coincide. Figure 5 clearly shows early drusen changes that are poorly defined in the fundus photograph (Figure 5A) and in the Maximum of the Parallel Detector Image (Figure 5E), but easily identified in spectral domain optical coherence tomography imaging (Figure 5C) and the Depolarized Light Image (Figure 5D).

Polarization sensitive optical coherence tomography is another promising technique for studying alterations to macular structure, combining aspects of scanning laser polarimetry and spectral domain optical coherence tomography. Polarization Sensitive optical coherence tomography has been shown capable of detecting irregularities in the polarization scrambling characteristics of the retinal pigment epithelium^{29,46–48} and other polarization changes such as birefringence,¹⁸ which cannot be differentiated using conventional *en face* imaging or reflectance spectral domain optical coherence tomography.¹⁹ Despite the better axial resolution in polarization sensitive optical coherence tomography, changes in the Depolarized Light Image continue to show features not visible in polarization sensitive optical coherence tomography imaging when directly compared, demonstrating the unique capabilities of scanning laser polarimetry imaging.¹⁹ Unlike the GDx used in this study to generate the Depolarized Light Image, polarization sensitive optical coherence tomography systems currently have a number of other limitations including increased complexity, longer acquisition times, and lack of accessibility, as polarization sensitive optical coherence tomography systems are not yet commercially available or in widespread clinical use.

With the introduction of new therapeutic interventions for retinal disease, accurate assessment of retinal health will become increasingly important. Techniques like scanning laser polarimetry could be useful in improving our understanding of the mechanisms behind age-related macular degeneration and improving our ability to detect changes earlier in the disease course. Improvements in both will be necessary for the future development of novel treatments, which could be implemented prior to extensive retinal damage and permanent vision loss.

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Figure 1.

Scanning laser polarimetry images from a subject with non-exudative age-related macular degeneration. (A) The Maximum Phase of the Crossed Detector Image demonstrates a relatively intact macular cross pattern used to localize the central fovea in other images derived from the same raw dataset. From the parallel detector, the maximum intensity over the entire image series at each pixel is used to create the Maximum of the Parallel Detector Image (B). This image emphasizes features that are primarily singly scattering or specularly reflecting, which are often the more superficial retinal features. From the crossed detector, the minimum in the modulation over the entire image series at each pixel is used to create the Depolarized Light Image (C). This image emphasizes features that multiply scatter, which includes the retinal pigment epithelium and pathological features commonly found in the deeper retina.

Figure 2.
(A) The Depolarized Light Image and (B) the Maximum of the Parallel Detector Image in a 71 year old control subject. (C) The Depolarized Light Image and (D) the Maximum of the Parallel Detector Image in a 71 year old subject with non-exudative age-related macular degeneration.

Figure 3.

The average coefficient of variation in image intensity over the central macula in each of the three image types used for analysis with 95% confidence intervals. The Depolarized Light Image showed a higher coefficient of variation in the age-related macular degeneration subjects than in the controls ($p=0.01$, marked with an asterisk). The Maximum of the Parallel detector image did not show differences in coefficient of variation between the two subject groups ($p=0.231$).

Figure 4.

(A) Fundus photograph demonstrating multiple small areas of early retinal pigment epithelium disruption localized in spectral domain optical coherence tomography, indicated by the numbered arrows. Because of the low contrast and lack of depth information, these changes are difficult to differentiate from other pathological features associated with age-related macular degeneration. (B) A scanning laser ophthalmoscope image from the Heidelberg Spectralis registered and cropped to match the orientation and dimensions of the scanning laser polarimetry-derived images. The green line in the scanning laser

ophthalmoscope image indicates the scan location for the middle of 3 consecutive spectral domain optical coherence tomography b-scan images acquired at 60 μm intervals (C). The scanning laser polarimetry derived Depolarized Light Image (D) and Maximum of the Parallel Detector Image (E). The numbered arrows correspond to the same location in each image type and localize areas of early retinal pigment epithelium disruption.

Figure 5.

(A) Fundus photograph of multiple areas of drusen localized in spectral domain optical coherence tomography, indicated by the numbered arrows. (B) A scanning laser ophthalmoscope with green lines indicating the scan location for spectral domain optical coherence tomography b-scan images (C). Spectral domain optical coherence tomography b-scans delineate drusen boundaries and can be used to differentiate drusen based on morphological characteristics. The spectral domain optical coherence tomography b-scans show elevations in the deep retinal structure, including the retinal pigment epithelium and

photoreceptor inner segment/outer segment junction. Small focal drusen with low internal reflectivity appear as localized areas with high intensity borders that surround a lower intensity central core in the Depolarized Light Image (D). The drusen borders in the Depolarized Light Image closely match the boundary of deep retinal elevations in spectral domain optical coherence tomography. In the Maximum of the Parallel Detector Image (E), these drusen appear as highly reflective in locations 2 and 3, but are difficult to differentiate due to low contrast in location 1. Similarly, drusen in location 1 are difficult to localize in the fundus photograph.

Figure 6.

A scanning laser ophthalmoscope image from the Heidelberg Spectralis (A), with a spectral domain optical coherence tomography b-scan (B). Spectral domain optical coherence tomography b-scans delineate the boundary of the druse and can be used to differentiate it based on morphological characteristics. The spectral domain optical coherence tomography b-scan show elevations in the deep retinal structure, including the retinal pigment epithelium and photoreceptor inner segment/outer segment junction. This large druse appears as a localized area with a high intensity border surrounding a lower intensity central core in the

Depolarized Light Image (C). The border in the Depolarized Light Image is much narrower than that in the Maximum of the Parallel Detector Image (D).

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Figure 7.

A scanning laser ophthalmoscope image from the Heidelberg Spectralis (A), and corresponding spectral domain optical coherence tomography b-scan (B). Spectral domain optical coherence tomography b-scans delineate the boundary of the hyper-reflective foci and several drusen along the scan line. The location of the large druse with overlying hyper-reflective foci in spectral domain optical coherence tomography b-scans also shows disruption to the retinal pigment epithelium and photoreceptor inner segment/outer segment junction. The large druse and overlying hyper-reflective foci are seen with high contrast as

high intensity features in the Depolarized Light Image (C), while other drusen along the scan line demonstrate high intensity borders surrounding a lower intensity central core. The borders of pathological features in the Depolarized Light Image match the boundaries of deep retinal elevations and hyper-reflective foci in spectral domain optical coherence tomography. In the Maximum of the Parallel Detector Image (D), the hyper-reflective foci in the spectral domain optical coherence tomography image is seen as highly reflective. Drusen in the Maximum of the Parallel Detector Image are variable and appear with lower contrast, with some drusen appearing as highly reflective, consistent with high reflectivity changes in the inner segment/outer segment junction overlying some drusen.

Figure 8.

A scanning laser ophthalmoscope image from the Heidelberg Spectralis (A), with a spectral domain optical coherence tomography b-scan (B). Spectral domain optical coherence tomography b-scans delineate the boundary of the subretinal deposits, accumulating between the retinal pigment epithelium and overlying photoreceptors. Subretinal deposits are seen as high intensity features with a lower intensity border that is irregular in the Depolarized Light Image (C). The border in the Depolarized Light Image closely match the boundaries of deep retinal elevations and debris accumulation seen in the spectral domain optical coherence

tomography b-scan. In the Maximum of the Parallel Detector Image (D), the subretinal deposits appeared as more uniform in intensity with low contrast.

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Figure 9.

(A) Fundus photograph of focal drusen (arrow 1), pigment clumping (arrow 2), and early retinal pigment epithelium disruption (arrow 3). The color information from the fundus photograph indicates an area of pigment clumping. A scanning laser ophthalmoscope image from the Heidelberg Spectralis (B), the scan location for spectral domain optical coherence tomography b-scan (C). The spectral domain optical coherence tomography b-scans (C) show disruptions to the deep retinal structure, corresponding to each of the 3 types of

changes, which are also seen in the fundus photograph and scanning laser polarimetry-derived images (D and E).

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