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OCT Changes Observed during the Progression of Early Age-Related Macular Degeneration

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Purpose: Automated retinal cell layer segmentation empowers OCT as a precise tool for characterizing morphologic features of retinal health throughout age-related macular degeneration (AMD) progression, particularly in advance of more visible biomarkers such as drusen and macular pigmentary changes. Few studies have examined OCT changes in eyes progressing from early to intermediate disease, or combined examinations of cell layer thickness, reflectivity, and heterogeneity. Therefore, this study analyzed OCTs from eyes progressing from early to intermediate AMD to identify changes in retinal morphology and reflectivity that may serve as biomarkers of early progression.

Design: Retrospective cohort study.

Participants: Patients $\geq$50 years with a diagnosis of AMD and with high-quality ipsilateral OCTs in both early and intermediate stage disease.

Methods: Fifty OCTs from 25 patients were automatically segmented using a previously validated artificial intelligence-driven algorithm. Changes in the mean and standard deviation of cell layer thickness and reflectivity with progression through stages were calculated for 90 retinal volumes with the help of a novel Python-based analysis tool.

Main Outcome Measures: The primary outcomes were significant changes to cell layer thickness, reflectivity, and heterogeneity with progression of AMD.

Results: With progression from early to intermediate disease, photoreceptor outer segments diffusely thinned. Within the ellipsoid zone, the fovea and parafovea were thinned with a simultaneous increase in thickness variability and a decrease in parafoveal reflectivity. The retinal pigment epithelium-Bruch's membrane complex underwent diffuse thickening and increased thickness variability alongside a decrease in foveal and parafoveal reflectivity.

Conclusions: These findings correlate with the known histopathology of early AMD and identify measurable OCT trends through the earliest stages of disease.

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Supplemental material available at www.ophthalmologyscience.org.

Age-related macular degeneration (AMD) is a significant cause of irreversible vision loss in the aging United States population.[1] The hallmark features of late AMD, including choroidal neovascularization and geographic atrophy, are collectively responsible for a majority of the visual impairment and blindness experienced by affected patients.[2] In contrast, the early and intermediate stages of AMD, as categorized by the Age-Related Eye Disease Study criteria, are characterized by relatively milder features including drusen and macular pigmentary changes, all of which may appear in advance of visual symptoms.[2,3] Among patients with early and intermediate AMD, continued focus has been placed on risk stratification for progression to advanced AMD, with the goal of identifying opportunities for early vision-sparing intervention.[4]

OCT has emerged as a potent tool for the detection and quantification of biomarkers of retinal health and AMD pathology, particularly alongside the development of reliable methods for automated retinal layer segmentation.[5–7] Pathognomonic features of the natural history of AMD including drusen development and progressive photoreceptor thinning have been reliably characterized with OCT imaging, both for the delineation of AMD relative to healthy subjects and for the monitoring of progression among affected individuals.[8–12] A growing list of OCT-specific biomarkers including OCT-reflective drusen substructures and hyperreflective foci have been proposed as signifiers of

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risk of progression from intermediate to late AMD.[4,13] The identification of reliable risk-stratifying OCT biomarkers is also important to inform the ongoing development and use of artificial intelligence-based models for prognosticating AMD.[14,15]

However, few studies of OCT imaging have examined in detail the natural history of progression through the earliest stages of AMD, especially in eyes where intermediate stage biomarkers such as OCT-reflective drusen substructures and hyperreflective foci may not yet have begun to appear. Whereas most studies concentrate on measures of the mean thickness of retinal cell layers, similarly few studies have incorporated measures of reflectivity, its topographical location, and the more subtle properties of variability in retinal cell layer thickness and reflectivity into their analyses. Since advanced AMD is largely irreversible, the ability to measure disease progression and risk-stratify from even the earliest signs of disease may have diagnostic and therapeutic implications, as any delay achieved in progression to intermediate disease may in turn offer a delay in the onset of advanced disease. Therefore, this study aimed to analyze eyes that progressed from early to intermediate AMD in order to identify significant changes in retinal morphology and reflectivity that can suggest patterns of early disease progression.

Methods

Study Participant and OCT Selection

This retrospective cohort study was comprised of patients with early and intermediate AMD. Institutional review board approval was obtained from the institutional review board at the Johns Hopkins University School of Medicine. Data were analyzed in a retrospective manner and consent was not required. All research adhered to the tenets of the Declaration of Helsinki.

The study population selection flowchart is shown in Figure 1. The initial sample was a randomized pool of 2500 patients with an International Classification of Diseases ninth or 10th revision code indicating a diagnosis of AMD and a Current Procedural Terminology code indicating receipt of an OCT during the years 2011 to 2021. Patients were excluded if they were <50 years of age, had a refractive error >-6 diopters, had Snellen visual acuity worse than 20/50, or had ever received a diagnosis of sickle cell disease, diabetes mellitus, a diabetic retinal disorder, a hereditary retinal dystrophy, or a retinal vascular occlusion. All codes used for population selection are listed in Supplemental Table S1 (available at https://www.ophthalmologyscience.org).

From the initial sample, patients with diagnosis codes for early AMD were identified (N = 314). Patients with no accessible OCT files (N = 96), with unusable OCT files due to quality or format (N = 16), with no eye having received $\geq$2 OCTs (N = 55), or who were found to have an erroneous diagnosis code (N = 8) were removed. To ensure accurate staging and identify patients with progression from early to intermediate AMD, images of the remaining patients (N = 139) were manually reviewed and staged according to the Age-Related Eye Disease Study categorization criteria,[3] with Age-Related Eye Disease Study category 2 and 3a defining early and intermediate AMD, respectively. Manual review yielded a set of 25 patients with high-quality ipsilateral OCTs with both early and intermediate disease. For consistency, the earliest valid OCT in each stage was downloaded, and eye laterality was chosen at random if OCTs from both eyes were available. Figure 2 shows a representative set of OCTs from 1 study participant.

OCT Analysis

OCTs were collected using Heidelberg SPECTRALIS instrumentation and a volume scan protocol, with 512 A-scans per B-scan and either 49 or 97 B-scans per volume (automated real time averaging of 9 frames). Prior to analysis, each patient's paired set of OCTs were confirmed to be of the same dimensions and capture settings to minimize systematic bias. OCTs were visualized using the Heidelberg Eye Explorer (Heyex) and segmented using the Iowa Reference Algorithms (Retinal Image Analysis Lab, Iowa Institute for Biomedical Imaging), the design and methods of which have been described previously.[5–7,12] The software allows for the automated identification and volumetric analysis of 11 retinal layers each divided into the 9 regions of the Early ETDRS macular grid (Fig 3). The ETDRS grid is divided into a 1-mm diameter foveal center, a 3-mm diameter inner macular ring, and a 6-mm diameter outer macular ring, forming regions which approximate to the 1.5-mm foveal, the 2.5-mm parafoveal, and the 5.5-mm perifoveal diameters. The segmentations of all OCTs included in this study were manually reviewed and adjusted where needed to ensure anatomic accuracy. Of note, the software does not specifically delineate and quantify drusen volume, and for the purposes of this analysis drusen volumes were included in the volumes ascribed to the retinal pigment epithelium-Bruch's membrane complex (RPE-BM) layer. Once segmentation was completed, the Iowa Reference Algorithms software was used to compute the mean and standard deviation (SD) of the thickness of each of the 99 retinal volumes described above.

To enable analysis of additional image properties including retinal layer reflectivity, a novel analysis tool was created using Python version 3.9.13 (Python Software Foundation). The tool intakes an OCT file in DICOM format along with the Iowa Reference Algorithms files defining the OCT segmentation surfaces and foveal center as input and performs calculations to determine the mean and SD of reflectivity in each retinal layer and ETDRS region. Because the component B-scans of an OCT are sequentially and not simultaneously collected, B-scans can be subject to unequal ambient conditions and may thus contain systematic differences in reflectivity and signal noise. To account for this possibility, the analysis tool normalizes the overall reflectivity of each B-scan relative to a specified retinal layer which is homogenized across the complete OCT. For this analysis, B-scan reflectivity was normalized relative to the ganglion cell layer due to its consistent and easily measured reflectivity and because it would be less expected to undergo significant reflectivity changes in early AMD. Similar to the Iowa Reference Algorithms, the analysis tool automatically computes the mean and SD of the reflectivity of each of the 90 defined retinal volumes. The subretinal virtual space was combined with the interdigitation zone because of a file formatting constraint.

Outcome Measures

The primary outcome measures of this study are the changes in the mean and SD of thickness and reflectivity in each retinal layer and ETDRS region with progression from early to intermediate AMD.

Statistical Analyses

To assess for changes in OCT properties with disease progression, pairwise *t* tests were performed for each property, comparing the 25 OCTs from early AMD with the corresponding 25 OCTs from intermediate AMD. Statistically significant changes were compiled

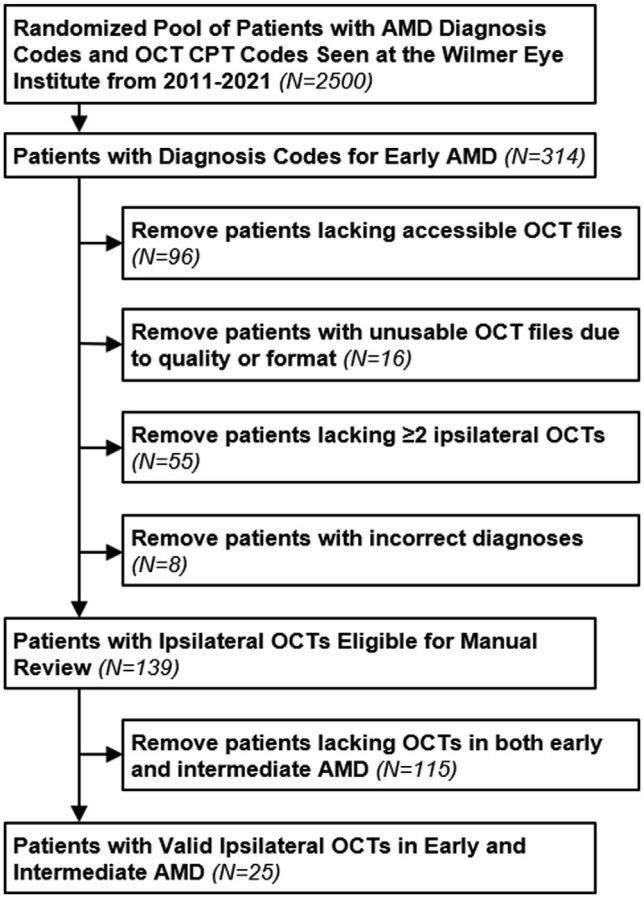

Figure 1. Population selection flowchart. AMD = age-related macular degeneration; CPT = Current Procedural Terminology.

and graphically presented. Statistical significance was set a priori at $P < 0.05$ for all analyses. All statistical analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing).

Results

Study Population Characteristics

The basic demographics of the study population are shown in Table 2. A total of 25 patients and 50 OCTs were included in the analysis. The study population was predominantly female (68%) and White (non-Hispanic) (92%). A relatively even sampling of right (44%) and left (56%) eyes was performed. The average (SD) age at which patients received their first OCT was 72.9 (8.25) and an average (SD) of 3.6 (2.00) years elapsed between the collection of the early and intermediate stage OCTs.

Changes in Retinal Layer Thickness with Progression from Early to Intermediate AMD

Figure 4 shows a schematic representation of the volumes defined by the retinal layers and ETDRS regions and the changes to those volumes as patients progressed from early to intermediate AMD. Supplemental Tables S3-S6 (available at https://www.ophthalmologyscience.org) provide the exact magnitude of these changes, expressed as the average percent change from early to intermediate AMD. Most notably, photoreceptor outer segment volumes significantly decreased in mean thickness in all ETDRS regions as patients progressed from early to intermediate AMD. In the ellipsoid zone (EZ), the mean thicknesses of the fovea and most of the parafoveal regions decreased with disease progression. The nasal and inferior parafoveal and perifoveal interdigitation zone experienced similar decreases. Retinal pigment epithelium-BM thickness was increased in all ETDRS regions with the progression from early to intermediate AMD.

Several retinal volumes had significant changes in the SD of their thickness as AMD progressed. Higher variability of RPE-BM thickness was observed in all ETDRS regions in intermediate relative to early AMD. Additionally, the variability of the parafoveal thickness of the subretinal virtual space was increased. The parafoveal photoreceptor inner segments and the parafoveal EZ both saw general increases to thickness variability with disease progression.

Changes in Retinal Layer Reflectivity with Progression from Early to Intermediate AMD

Several changes in retinal layer reflectivity were observed with disease progression, albeit with fewer broad trends than

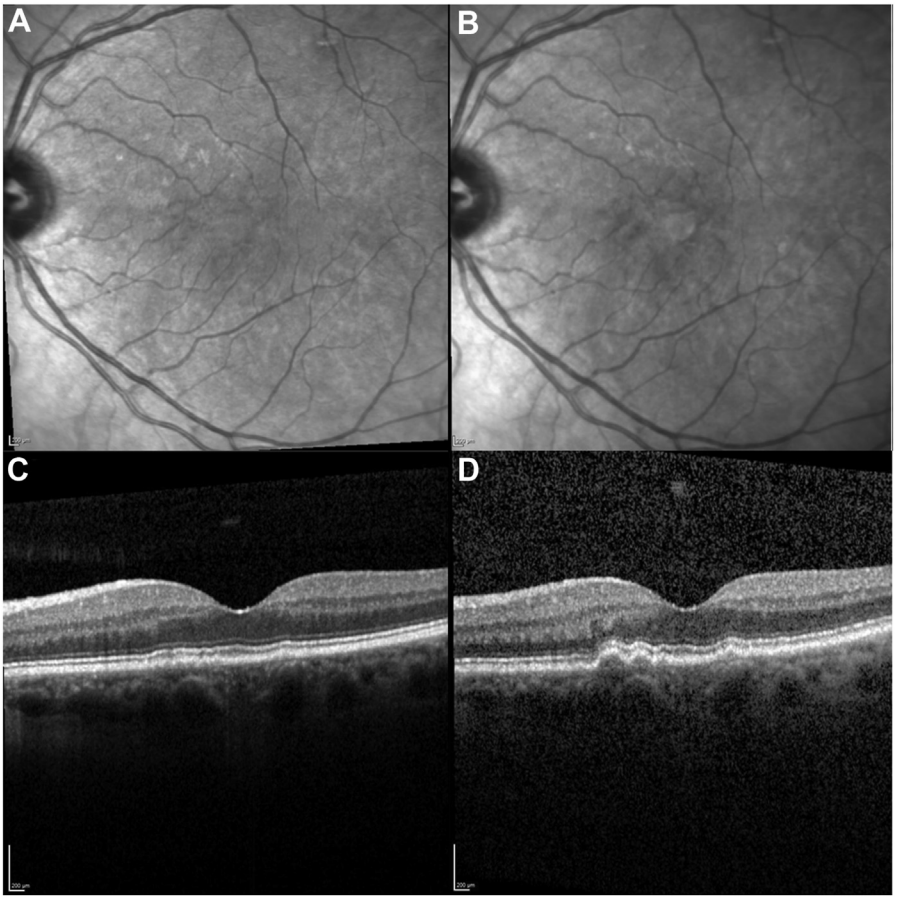

Figure 2. Representative en face (**A**, **B**) and macular cross-section (**C**, **D**) images sampled from ipsilateral OCT scans of a single patient during the early (**A**, **C**) and intermediate (**B**, **D**) stages of age-related macular degeneration.

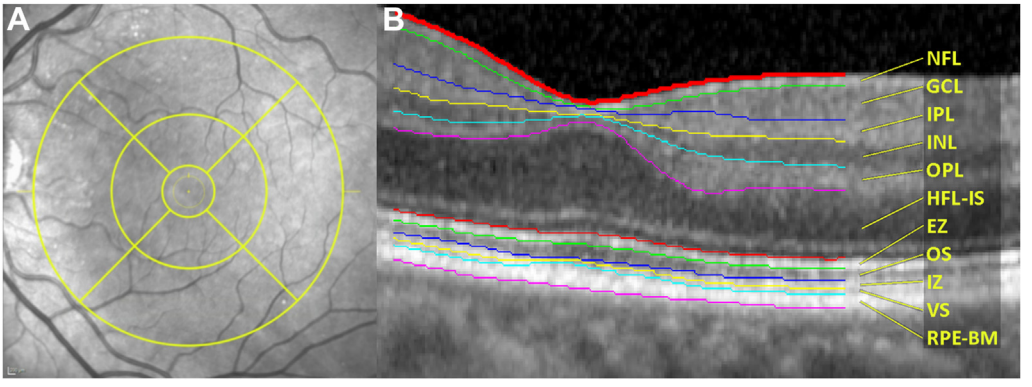

Figure 3. Representative images from automated retinal layer segmentation process. **A**, Placement of ETDRS grid to define macular regions with diameters of 1-mm (foveal center), 3-mm (inner macula), and 6-mm (outer macula). **B**, Sample cross section of segmentation result using Iowa Reference Algorithms software. Colored lines indicate automatically generated segmentation surfaces. EZ = ellipsoid zone; GCL = ganglion cell layer; HFL-IS = Henle fiber layer through photoreceptor inner segment; INL = inner nuclear layer; IPL = inner plexiform layer; IZ = interdigitation zone; NFL = nerve fiber layer; OPL = outer plexiform layer; OS = photoreceptor outer segment; RPE-BM = retinal pigment epithelium and Bruch's membrane; VS = subretinal virtual space.

Table 2. Basic Demographics of Study Population (N = 25)

Characteristic	N (%) or Mean [SD]
Sex	
Male	8 (32)
Female	17 (68)
Race and ethnicity	
White (non-Hispanic)	23 (92)
Black (non-Hispanic)	1 (4)
Other/Not specified	1 (4)
Eye used in analysis	
OD	11 (44)
OS	14 (56)
Age at receipt of OCT (yrs)	
Early stage	72.9 [8.25]
Intermediate stage	76.5 [8.05]
Time elapsed between OCTs (yrs)	
Mean	3.64 [2.00]

OD = right eye; OS = left eye; SD = standard deviation.

were observed in retinal layer thicknesses. Three parafoveal regions of the EZ experienced a significant decrease in mean reflectivity with progression to intermediate AMD. In the RPE-BM, the fovea and parafovea exhibited significantly lower reflectivity in intermediate AMD compared with early disease.

Discussion

This study investigated changes in the OCT parameters of both retinal layer thickness and reflectivity by anatomic location during progression from early to intermediate AMD. While most studies to date have focused on OCT features associated with progression beyond intermediate AMD, the mean 3.6 years observed here between early and intermediate stages highlights a period prior to the development of more classic OCT features of AMD. Although not all patients with AMD will progress,[2] the detection of features that develop in early disease might be helpful in identifying the most at-risk patients, especially in patients who develop these changes over a short time interval.

Curcio et al found that rod photoreceptor loss in the parafoveal macula was one of the first alterations of early AMD.[16] In this study, rod photoreceptor outer segments underwent diffuse thinning with disease progression. This histopathologic assessment correlates with OCT studies that have identified photoreceptor thinning in early or intermediate AMD compared with healthy controls[17,18] or photoreceptor thinning that is proportional to underlying drusen volume.[18–20] It is also possible that the decreased mean thicknesses observed in our study, given the early stage at which OCTs were captured, do not represent outright photoreceptor degeneration, but could alternatively represent early histologic changes including photoreceptor disorganization[21] or compression[22] that have been noted in adaptive optics OCT[21] and histologic[22] investigations of early AMD. Regardless, these results suggest that parafoveal photoreceptor layer thinning can be observed clinically at an early AMD stage.

The highly reflective EZ band is a notable OCT representation of the dense mitochondria aggregation within photoreceptor inner segments.[23] In our study, we observed that both the EZ thickness and reflectivity decreased in the parafovea with progression from early to intermediate disease, which suggests loss and disorganization of photoreceptor mitochondria. Given the importance of mitochondria for maintaining the high metabolic needs of photoreceptors, mitochondrial loss could herald further photoreceptor dysfunction and death as seen by the continued decrease of EZ thickness and reflectivity, especially in the parafovea, as identified by Curcio et al.[16] We were also intrigued by the increased variability in parafoveal EZ thickness measurements. Cellular heterogeneity and irregularity has been identified in AMD,[21] and the EZ thickness variation observed here could represent photoreceptor heterogeneity due to different stages of dysfunction and survival. That relatively few regions overall underwent significant changes in variability of thickness or reflectivity suggests that the precision of thickness and reflectivity measurements was not overly impacted by drusen disruption of retinal organization during disease progression. Further characterization of photoreceptor heterogeneity in early disease will be important, as disruption and irregularity in the EZ layer was already identified as a risk for progression to advanced AMD by a previous study.[24]

Accompanying photoreceptor thinning, we observed an increase in RPE-BM mean thickness and variability in all regions with progression from early to intermediate AMD, and a decrease in the reflectivity of the foveal and parafoveal RPE-BM. While drusen were included in the RPE-BM volume calculation during automated segmentation, likely accounting for much of the widening and heterogeneity, we also observed general RPE-BM expansion in regions not affected by drusen. In these areas distinct from frank drusen, changes to RPE-BM thickness and heterogeneity could reflect the broader life cycle of drusen, with RPE-BM thickening in anticipation of drusen appearance and with subsequent thinning as drusen mature and disappear.[18,20] The variability of RPE-BM thickness could also be due to retinal pigment epithelium (RPE) morphologic heterogeneity, which is a well-documented change in AMD.[25] Likewise, the decrease in RPE-BM reflectivity in the fovea and parafovea could reflect structural or molecular alterations in the RPE during AMD progression. Our lab has correlated these morphologic changes with molecular changes in the RPE.[26] The preferential parafoveal location of these RPE-BM reflectivity changes is in the same location as the photoreceptor changes that are seen in early AMD.[16] These superimposed RPE and photoreceptor changes may reflect the reliance of photoreceptor health on the RPE. The combined examination of morphology and reflectivity may enable us to capture nuanced structural changes using OCT that correspond with cellular pathophysiology. The early changes observed here in the foveal and parafoveal RPE-BM may be linked with progression to involve cone-rich regions, as prior studies have shown that increased RPE-drusen complex volume is

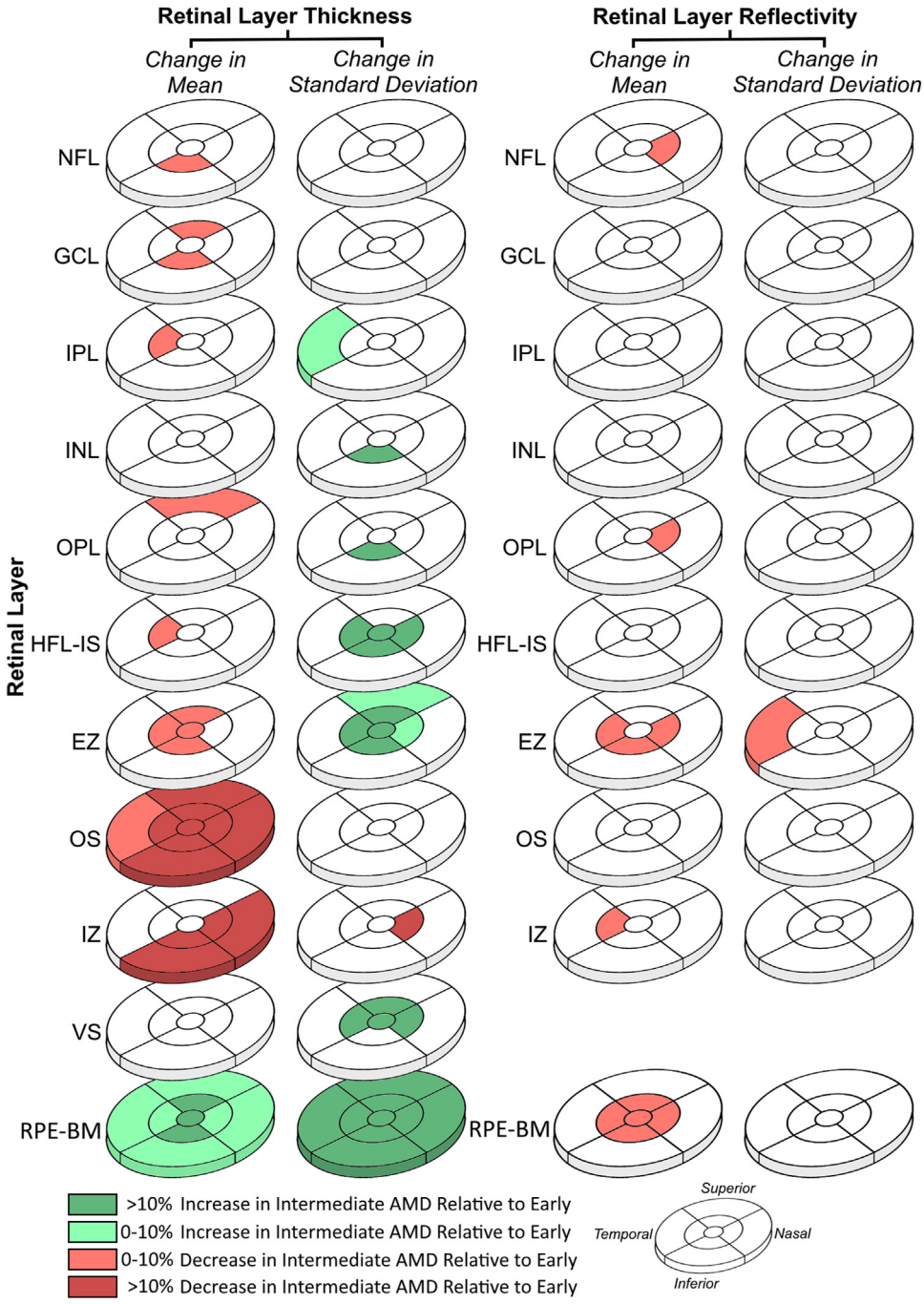

Figure 4. Schematic depiction of significant changes ($P < 0.05$) in OCT properties with progression from early to intermediate stage AMD, organized by ETDRS region and retinal layer. Light green coloration indicates a property significantly increased in the specified region with disease progression, while light red coloration indicates a property significantly decreased. Additional dark green or dark red coloration indicates a >10% increase or decrease, respectively. Top quadrants of ETDRS grid schematics correspond to the superior aspect of the retina, bottom to inferior, left to temporal, and right to nasal. AMD = age-related macular degeneration; EZ = ellipsoid zone; GCL = ganglion cell layer; HFL-IS = Henle fiber layer through photoreceptor inner segment; INL = inner nuclear layer; IPL = inner plexiform layer; IZ = interdigitation zone; NFL = nerve fiber layer; OPL = outer plexiform layer; OS = photoreceptor outer segment; RPE-BM = retinal pigment epithelium and Bruch's membrane; VS = subretinal virtual space.

associated with impaired visual function including visual acuity,[27,28] contrast sensitivity,[29] and dark-adaptation time.[27] Future work should continue to investigate the histopathologic correlations of RPE reflectivity in the setting of drusen accumulation and photoreceptor degeneration in early AMD.

While our OCT findings correlated with known histopathologic changes, this study has several limitations.

The relatively small sample size and large number of parameters studied increases the possibility of spurious results. Random signal noise may have contributed to isolated regions of significance, particularly in the inner retina, although the cohesive magnitude of change and contiguous area of effect demonstrated in the outer retinal changes would be less likely be explained by simple random chance. Although automated OCT segmentations were manually reviewed and corrected where necessary, the relatively small volumes studied in the outer retina increase the magnitude of any errors in segmentation of these retinal layers. Because our study is observational, further work is required to establish the extent that the patterns of cellular morphology identified here will predict progression of early to intermediate AMD.

This study identifies specific OCT properties of retinal cell layers including mean thickness, variability in thickness, and mean reflectivity that undergo changes in the progression from early to intermediate AMD. These changes correlate with the known histopathology of RPE and rod changes in the parafovea in early AMD. The decreased EZ thickness and reflectivity in the parafovea suggests rod photoreceptor degeneration. Likewise, the diffuse RPE-BM thickening and variability in the parafovea observed here, while likely primarily due to drusen accumulation, could also reflect the morphologic and molecular heterogeneity that is seen in early AMD. Future work is required to correlate these patterns with the known histopathology of early AMD and with markers for risk of progression to advanced disease.

Footnotes and Disclosures

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

J.T.H.: Consultant − Seeing Medicines, Inc.; SAB-vested stock − Character Biosciences, Inc., Cirrus Pharmaceuticals, Inc.

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HUMAN SUBJECTS: Human subjects were included in this study. Institutional review board approval was obtained from the institutional review board at the Johns Hopkins University School of Medicine. Data were analyzed in a retrospective manner and consent was not required. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Heckenlaible, Toomey, Handa

Data collection: Heckenlaible

Analysis and interpretation: Heckenlaible, Handa

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Overall responsibility: Heckenlaible, Toomey, Handa

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **EZ** = ellipsoid zone; **RPE** = retinal pigment epithelium; **RPE-BM** = retinal pigment epithelium/Bruch's membrane complex; **SD** = standard deviation.

Keywords:
Age-related macular degeneration, Artificial intelligence, Biomarkers, OCT.

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References

1. Klein R. Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol*. 2011;129:75.
2. Flores R, Carneiro Â, Vieira M, et al. Age-related macular degeneration: pathophysiology, management, and future perspectives. *Ophthalmologica*. 2021;244:495−511.
3. The age-related eye disease study (AREDS). *Control Clin Trials*. 1999;20:573−600.
4. Flores R, Carneiro Â, Tenreiro S, Seabra MC. Retinal progression biomarkers of early and intermediate age-related macular degeneration. *Life*. 2021;12:36.
5. Abramoff MD, Garvin MK, Sonka M. Retinal imaging and image analysis. *IEEE Rev Biomed Eng*. 2010;3:169−208.
6. Li Kang, Wu Xiaodong, Chen DZ, Sonka M. Optimal surface segmentation in volumetric images-A graph-theoretic approach. *IEEE Trans Pattern Anal Mach Intell*. 2006;28:119−134.
7. Garvin MK, Abramoff MD, Xiaodong Wu, et al. Automated 3-D intraretinal layer segmentation of macular spectral-domain optical coherence tomography images. *IEEE Trans Med Imaging*. 2009;28:1436−1447.
8. Pollreisz A, Reiter GS, Bogunovic H, et al. Topographic distribution and progression of soft drusen volume in age-related macular degeneration implicate neurobiology of fovea. *Invest Ophthalmol Vis Sci*. 2021;62:26.

9. Yehoshua Z, Wang F, Rosenfeld PJ, et al. Natural history of drusen morphology in age-related macular degeneration using spectral domain optical coherence tomography. *Ophthalmology*. 2011;118:2434−2441.
10. Schlanitz FG, Baumann B, Kundi M, et al. Drusen volume development over time and its relevance to the course of age-related macular degeneration. *Br J Ophthalmol*. 2017;101:198−203.
11. Farsiu S, Chiu SJ, O'Connell RV, et al. Quantitative classification of eyes with and without intermediate age-related macular degeneration using optical coherence tomography. *Ophthalmology*. 2014;121:162−172.
12. Sun JQ, McGeehan B, Firn K, et al. Comparison of the Iowa Reference Algorithm to the Heidelberg Spectralis optical coherence tomography segmentation algorithm. *J Biophotonics*. 2020;13:e201960187.
13. Waldstein SM, Vogl WD, Bogunovic H, et al. Characterization of drusen and hyperreflective foci as biomarkers for disease progression in age-related macular degeneration using artificial intelligence in optical coherence tomography. *JAMA Ophthalmol*. 2020;138:740.
14. Muntean GA, Marginean A, Groza A, et al. The predictive capabilities of artificial intelligence-based OCT analysis for age-related macular degeneration progression—a systematic review. *Diagnostics*. 2023;13:2464.
15. Romond K, Alam M, Kravets S, et al. Imaging and artificial intelligence for progression of age-related macular degeneration. *Exp Biol Med*. 2021;246:2159−2169.
16. Curcio C, Medeiros NE, Millican CL. Photoreceptor loss in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 1996;37:1236−1249.
17. Brandl C, Brücklmayer C, Günther F, et al. Retinal layer thicknesses in early age-related macular degeneration: results from the German AugUR study. *Invest Ophthalmol Vis Sci*. 2019;60:1581.
18. Nivison-Smith L, Wang H, Assaad N, Kalloniatis M. Retinal thickness changes throughout the natural history of drusen in age-related macular degeneration. *Optom Vis Sci*. 2018;95:648−655.
19. Schuman SG, Koreishi AF, Farsiu S, et al. Photoreceptor layer thinning over drusen in eyes with age-related macular degeneration imaged in vivo with spectral-domain optical coherence tomography. *Ophthalmology*. 2009;116:488−496.e2.
20. Rogala J, Zangerl B, Assaad N, et al. In vivo quantification of retinal changes associated with drusen in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2015;56:1689−1700.
21. Reumueller A, Schmidt-Erfurth U, Salas M, et al. Three-dimensional adaptive optics−assisted visualization of photoreceptors in healthy and pathologically aged eyes. *Invest Ophthalmol Vis Sci*. 2019;60:1144.
22. Spaide RF, Curcio CA. Drusen characterization with multimodal imaging. *Retina*. 2010;30:1441−1454.
23. Litts KM, Zhang Y, Freund KB, Curcio CA. Optical coherence tomography and histology of age-related macular degeneration Support mitochondria as reflectivity sources. *Retina*. 2018;38:445−461.
24. Ferrara D, Silver RE, Louzada RN, et al. Optical coherence tomography features preceding the onset of advanced age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2017;58:3519.
25. Curcio CA, Zanzottera EC, Ach T, et al. Activated retinal pigment epithelium, an optical coherence tomography biomarker for progression in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2017;58:BIO211−BIO226.
26. Datta S, Cano M, Satyanarayana G, et al. Mitophagy initiates retrograde mitochondrial-nuclear signaling to guide retinal pigment cell heterogeneity. *Autophagy*. 2023;19:966−983.
27. Sevilla MB, McGwin G, Lad EM, et al. Relating retinal morphology and function in aging and early to intermediate age-related macular degeneration subjects. *Am J Ophthalmol*. 2016;165:65−77.
28. Pondorfer SG, Wintergerst MWM, Gorgi Zadeh S, et al. Association of visual function measures with drusen volume in early stages of age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2020;61:55.
29. Ghoshal R, Sharanjeet-Kaur S, Mohamad Fadzil N, et al. Correlation between visual functions and retinal morphology in eyes with early and intermediate age-related macular degeneration. *Int J Environ Res Public Health*. 2020;17:6379.