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Baseline Spectral Domain Optical Coherence Tomography Characteristics of Age-Related Macular Degeneration

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Abstract

Purpose: To describe spectral domain optical coherence tomography (SD-OCT) findings in an Amish cohort to assess SD-OCT markers for early age-related macular degeneration (AMD).

Methods: The authors performed a family-based prospective cohort study of 1,146 elderly Amish subjects (age range 50–99 years) (2,292 eyes) who had a family history of at least 1 individual with AMD. All subjects underwent complete ophthalmic examinations, SD-OCT using both Cirrus and Spectralis (20 × 20° scan area) instruments, fundus auto-fluorescence, infrared imaging, and color fundus photography. Spectral domain optical coherence tomography characteristics were analyzed in subjects with AMD (with and without subretinal drusenoid deposits [SDDs]) and normal healthy cohorts.

Results: Participants' mean age was 65.2 years (SD ± 11). Color fundus photographic findings in 596 (53%) subjects (1,009 eyes) were consistent with AMD; the remaining 478 (43%) subjects showed no signs of AMD. The choroid was significantly thinner on OCT ($242 \pm 76 \mu\text{m}$, $P < 0.001$) in those with AMD compared with those without ($263 \pm 63 \mu\text{m}$). Subretinal drusenoid deposits

were found in 143 eyes (7%); 11 of the 143 eyes (8%) had no other manifestations of AMD. Drusen volume ($P < 0.001$) and area of geographic atrophy ($P < 0.001$) were significantly greater, and choroid was significantly ($P < 0.001$) thinner in subjects with SDDs versus those without SDDs.

Conclusion: The authors describe spectral domain optical coherence tomography characteristics in an elderly Amish population with and without AMD, including the frequency of SDD. Although relatively uncommon in this population, the authors confirmed that SDDs can be found in the absence of other features of AMD and that eyes with SDDs have thinner choroids.

Keywords

Amish population; spectral domain optical coherence tomography; subretinal drusenoid deposits

Age-related macular degeneration (AMD) is influenced by genetic, environmental, and dietary factors and is the leading cause of irreversible vision loss in individuals aged 65 years and older in the developed world.^{1,2} The rising prevalence of AMD is presumably driven by an aging population. Vision loss caused by AMD is divided into two categories: nonneovascular or dry AMD and neovascular or wet AMD.³ Dry AMD is characterized by the presence of drusen, hyper- or hypopigmentation of the retinal pigment epithelium (RPE), and in later stages, geographic atrophy (GA).^{4,5} Drusen, particularly large soft drusen, are a distinguishing feature and a characteristic physical sign of nonneovascular AMD.^{6,7} Neovascular AMD occurs when new blood vessels invade Bruch's membrane and produce exudation in the macula.^{3,4}

There is substantial variation in the progression from early to late AMD^{8,9}; consequently, the factors influencing this progression are not completely understood. Dietary supplements provide some reduction in the progression of AMD.¹⁰ Although anti-VEGF therapy can be an effective treatment for the neovascular form of AMD, it is not a cure. In addition, a significant minority of those with choroidal neovascularization fail to respond to anti-VEGF treatments.^{11–13} Thus, it is critical to understand the underlying causes of early AMD to enable discoveries of new therapies directed at the earlier stages of the disease.

A potential impediment to the identification of new therapies is the current AMD classification. The clinical disease classification of AMD, obtained by phenotyping the anatomical changes detected by clinical examination and/or fundus photographs do not reflect the biological underpinnings of AMD, which are poorly understood. In addition, these older methods of classifying AMD are not always sensitive enough to detect some of the anatomical changes of AMD. For example, the presence and location of subretinal drusenoid deposits (SDDs) are difficult to detect on a fundus photograph or clinical examination. Today, SDDs can be detected during the early stages of AMD with fundus autofluorescence (FAF), infra-red reflectance (IR), or optical coherence tomography (OCT).

The high resolution, sensitivity, and speed of spectral domain optical coherence tomography (SDOCT) have enabled detailed visualization of the outer retinal and subretinal substructures.^{14,15} The combined use of color fundus photographs and SD-OCT is routine for clinical trials and population-based studies.^{5,16,17}

The Amish Eye Study was initiated to identify biomarkers of OCT for earlier stages of AMD in a family-based cohort; to assess the heritability of identified OCT biomarkers in the families; and to sequence the DNA from these families to identify rare/ moderate genetic variants that associate with the identified AMD biomarkers. Our family-based approach to quantifying SD-OCT biomarkers associated with AMD will provide information on the heritability of that marker and its potential for genetic studies.¹⁸ We have intentionally focused on the Amish population because it is a founder population and they are genetically and culturally isolated, and thus experience a relatively uniform environment and reduced genetic diversity. That represents an isolate with less genetic and environmental variation than the general population. As a result, the background heterogeneity between individuals will be reduced. In addition, the Amish do not indulge in significant smoking behavior, thereby reducing the amount of AMD risk attributable to smoking in this sample.

The Amish Eye Study is recruiting Amish subjects from the three largest Amish communities in the United States.: Holmes County, Ohio; Elkhart and LaGrange Counties, Indiana^{19,20} and Lancaster Counties, Pennsylvania.²¹ These communities are collectively an isolated founder population originating from two waves of immigration of Swiss Anabaptists into the United States in the 1700s and 1800s. The first wave of immigration brought the Anabaptists to Lancaster County, Pennsylvania. In the early 1800s, some of these immigrants moved to Holmes County, Ohio,²² whereas a second wave of immigration from Europe established Amish communities in Ohio (including Wayne County but not Holmes County) and Indiana (including Adams County).²¹ Starting in 1841, the Elkhart and LaGrange Counties Amish community was founded by Amish families primarily from Somerset County, Pennsylvania, and from Holmes and Wayne Counties, Ohio, who were seeking a new farmland.²³

The present study describes our recruitment and phenotyping strategy, particularly focused on OCT for screening a family-based prospective cohort that can be used to identify SD-OCT markers for early AMD.

Methods

Ascertainment and Eligibility

Participants were identified from three settlements in Ohio, Indiana, and Pennsylvania. Human subject protocols have been approved by the Institutional Review Boards of the University of Pennsylvania, University of Miami, Case Western Reserve University, and University of California—Los Angeles. All study procedures followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study. Inclusion criteria for a subject to the study were age ≥ 50 years, self-identification as Amish, and membership in a sibship with at least 1 individual reported to have AMD. Exclusion criteria included inadequate image quality or any previous or concomitant ophthalmological condition that could confound the interpretation of AMD features on imaging. Data reported in this manuscript were collected between February 2013 and July 2016.

Study Procedures

The clinical examination included an on-site ophthalmic examination, interview, and venipuncture. Examination data were recorded on examination forms and then entered directly into the Amish Eye Study database at the University of Miami. Data collection was standardized and included measurements taken by clinical research coordinators, ophthalmic technicians, and board-certified ophthalmologists in respective study sites. The examination included 1) name, age, date of birth, sex, address, parents' and siblings' names and addresses, family history of AMD, and the presence of any other eye diseases; 2) visual acuity, measured using a Snellen chart at 20 feet; 3) flash color fundus photography with a Topcon camera; 4) fundus examination by direct and indirect ophthalmoscopy; and 5) SD-OCT.

Spectral domain optical coherence tomography imaging at all sites was performed on two instruments: Cirrus OCT (Carl Zeiss Meditec Inc, Dublin, CA) and Spectralis (HRA + OCT; Heidelberg Engineering, Inc, Heidelberg, Germany) using macular cube scan protocols on both eyes. Images were acquired from both devices to take advantage of unique capabilities of each, automated quantification of features such as drusen by the Cirrus, and better visualization of the outer retinal substructures and choroid by the averaged scans of the Spectralis.

The Cirrus OCT scans were acquired using a macular cube protocol of 512 by 128 (128 B-scans and 512 A-scans per B-scan) over a 6 mm × 6 mm area centered on the fovea. The Spectralis acquisition protocol consisted of a 512 × 97 macular volume cube (97 B-scans and 512 A-scans per B-scan, ART of nine frames) over a 20 × 20° (6 mm × 6 mm) field centered on the fovea. Sub-retinal drusenoid deposits have been described to commonly be found outside the central macula, often along the arcades or even nasal to the optic nerve. Thus, similar volume cube scans were also obtained with both devices centered on the optic nerve. Enhanced depth imaging was not obtained; however, the operators did orient the OCT image closer to the vitreous side to minimize distance from the zero delay line. Enhanced depth imaging was not obtained to simplify procedures for the operator and patient and because the choroid was expected to be relatively thinner in this elderly population. Subfoveal choroidal thickness was measured using instrument calipers in both the Spectralis and Cirrus acquisitions. However, a priori, only the Spectralis-derived choroidal thickness was used for further analysis. Eyes in which the choroidal-scleral boundary could not be identified were marked "could not be graded" and were not included in the quantitative analysis. Choroidal thickness could not be graded in 96 (4%) eyes by the Spectralis and 211 (9%) eyes by the Cirrus.

To assess the reproducibility of our readings, we evaluated inter- and intragrader correlation by randomly selecting 240 eyes from 120 subjects and having 2 independent graders who were masked to the previous results of choroidal thickness measurements.

Automated quantification of drusen area, volume, and GA area within the macular cube was performed using the Cirrus 6.2 software RPE analysis segmentation algorithms.^{14,24} The automated GA segmentation was inspected, and segmentation errors were manually corrected to generate GA areas. Geographic atrophy on SD-OCT was identified as a region

where choroidal hypertransmission was detected with RPE loss. Drusen measurements were analyzed in 3-mm and 5-mm rings centered on the fovea (Figure 1). Geographic atrophy area was measured in a 5-mm ring centered on the fovea.

Qualitative parameters such as the presence or absence of intra- and subretinal fluid (hyporeflective pockets of fluid), subretinal hyperreflective material, outer retinal tubulations, SDDs, and presence and axial extent of intraretinal hyperreflective foci (HRF) were analyzed by evaluating all the B-scans in SD-OCT volumes. Of note, subretinal hyperreflective material was diagnosed if there was any bright material between the outer border of the photoreceptors and the RPE (Figure 2). Because no fluorescein angiography was obtained, it was not possible to determine with certainty whether subretinal hyperreflective material corresponded to vitelliform-like accumulations or was related to an exudative process. If HRF were present, the innermost retinal layer to which the HRF extended was documented as LHRF (level of HRF). Retinal layers included in the LHRF classification were the photoreceptor segment (inner and outer) layers, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, and ganglion cell layer.²⁵ Qualitative assessment of the presence or absence of pigment epithelial detachment and the pigment epithelial detachment subtype based on internal reflectivity characteristics (drusenoid, fibrovascular, or serous) was assessed in each eye.^{26,27} Subretinal drusenoid deposits were identified as hyperreflective elevations above the RPE or in line with the photoreceptor outer segments. Our OCT scanning area for the detection of SDDs was more limited in the field of view (despite inclusion of both macula-centered and optic nerve-centered scans) (Figure 3) as compared to the recommended regions we scanned by IR or FAF imaging.²⁸

Blue-light FAF and IR imaging were performed using the Spectralis HRA + OCT with a 30° image centered on the fovea (Field 2) and the optic nerve position at the nasal edge of the image. Images with poor quality because of focus, exposure, or artifacts were excluded from the study analysis. All images were analyzed by a trained, certified, senior Doheny Image Reading Center grader. The OCT data from the two devices were graded separately in a masked fashion to identify any discrepancies in assessment between instruments.

Color fundus photographs were evaluated for the presence, number, and size of drusen, as well as for pigment alterations. The diagnosis of AMD in an eye was determined according to the Beckman classification,²⁹ which requires a minimum of five medium-sized drusen ($\geq 63 \mu\text{m}$) on a color fundus photograph. Eyes with no abnormalities, only small hard drusen, or fewer than five medium drusen were considered to be unaffected.

Statistical Analysis

The descriptive statistics were performed using all eyes for the main outcome measures for this study including drusen area, drusen volume, GA choroidal thickness, and qualitative parameters as described in Table 1. The correlations of quantitative parameters were assessed using all subjects available after adjusting for the age at examination and sex. To adjust for the influence of sibship among subjects, the multivariate familial correlations were estimated using the method by Keen and Elston³⁰ and Matthew et al.,³¹ as implemented in the FCOR program in the Statistical Analysis for Genetic Analysis (S.A.G.E.) package.³² To

compare age-and sex-adjusted phenotype mean values with different groups defined by SDD status or by AMD status, the mean of two measurements from the right and left eyes was used and the generalized estimating equation method was used to adjust for correlations because of the related subjects. A *P* value of <0.05 was considered statistically significant. All statistical analyses besides familial correlations were performed using SPSS 18 statistical software (SPSS version 18.0, IBM, Chicago, IL).

Results

Recruitment and Ascertainment

A total of 1,146 (2,292 eyes) participants were recruited to the Amish Eye Study from February 2013 and July 2016. A total of 2,191 eyes (95.6%) of 1,124 subjects met the OCT-including criteria for the qualitative analysis after excluding 101 eyes (4.4%) because of the poor quality scans or significant (>10% of drusen area) drusen segmentation errors, or missing scans on the SD-OCT. For each quantitative variable, additional eyes were excluded. For example, choroidal thickness could not be graded in 96 eyes (4%) by the Spectralis and 211 eyes (9%) by the Cirrus. Among 2,191 eyes, 1,009 eyes (46.1%) had fundus photograph grades consistent with AMD and 1,048 eyes (49.4%) had no AMD. Age-related macular degeneration status could not be determined for 98 eyes (4.5%). In addition, 444 of 1,124 subjects (40%) had AMD in both eyes (affected cohort), 152 subjects (14%) had AMD in 1 eye only, and 478 subjects (43%) had no AMD (unaffected cohort). There were 2,282 sibpairs from 377 sibships of size 1 to 13 in which 158 of them were without any additional sibs, that is, 14% of data were of independent subjects.

Baseline Characteristics

The mean age of the 1,146 participants was 65.2 ± 11 (mean $\pm$ SD) years with a slight majority being women (60%). The mean age of the 478 unaffected cohort was 62.1 ± 9.5 years, whereas AMD-affected subjects were older with an average age of 68.1 ± 11.4 years ($P < 0.001$).

Table 1 shows frequencies of abnormalities found by SD-OCT. Subretinal fluid and fibrovascular pigment epithelial detachments were relatively uncommon (less than 2%), reflecting the low prevalence of neovascular disease in our population. Aside from drusenoid lesions, the most common abnormalities on OCT in this cohort were intraretinal hyperreflective features, which are believed to correspond to pigment migration on color photographs and can be seen over-lying some drusen. Hyperreflective foci over drusen were seen in nine of the eyes (Figure 2B) and had extended to the outer nuclear layer or further internally in the vast majority of cases.

The SD-OCT measurements for drusen area, volume, and choroidal thickness in subjects with AMD are described in Table 2. The mean drusen area was 0.22 mm^2 and 0.39 mm^2 for the 3- and 5-mm circles, respectively. The mean drusen volume was 0.01 mm^3 for the 3-mm circle and 0.02 mm^3 for the 5-mm circle. The mean GA area in the 5-mm circle zone was 0.47 mm^2 (Table 2). Considering only those eyes with GA ($N = 99$ eyes), the mean GA area was $5.32 \pm 5.91 \text{ mm}^2$. The mean choroidal thickness for all eyes was $255 \pm 70 \mu\text{m}$ (range:

14–439 μm). After adjusting for age, in subjects with AMD, the mean choroidal thickness was significantly less ($242 \pm 76 \mu\text{m}$, $P < 0.001$) when compared with those with no AMD ($263 \pm 63 \mu\text{m}$).

There was a significant correlation ($P < 0.001$) between the right and left eyes with respect to drusen area, drusen volume, GA, and choroidal thickness measurements (Table 2). Only choroidal thickness measurements had significant intraclass correlations ($P < 0.001$) among sibpairs but not on drusen area and volume variables in subjects with AMD.

Reproducibility Analysis

Intragrader Reproducibility.—The mean choroidal thickness for the first and second gradings were $250 \pm 79 \mu\text{m}$ and $253 \pm 79 \mu\text{m}$, respectively, with a mean absolute difference of $10 \pm 8 \mu\text{m}$ (maximum; 41). The ICC was 0.994 ($P < 0.001$) (95% confidence interval: 0.993–0.995) (Figure 4).

Intergrader Reproducibility.—The mean cystoid space volumes computed by grader 1 and grader 2 were $250 \pm 79 \mu\text{m}$ and $253 \pm 78 \mu\text{m}$, respectively, with a mean absolute difference of 7 ± 7 (maximum; 45). The ICC was 0.996 ($P < 0.001$) (95% confidence interval: 0.995–0.997) (Figure 4).

The presence of SDDs was assessed in all study eyes using both the Cirrus and Spectralis OCT and both the macula and optic nerve–centered cube scans combined. Subretinal drusenoid deposits could be observed in 32 (1.5%) eyes with the Cirrus and in 68 (3.1%) eyes with the Spectralis, with discordant findings between devices for 41 (1.9%) eyes. Of note, when assessing for SDDs with IR and FAF imaging, which also covered a larger total field of view than the OCT scans, the prevalence rose to 7% or 143 of eyes. Of 143 eyes with SDDs, 11 were classified as normal. Drusen volume ($P < 0.001$) and GA area ($P < 0.001$) were significantly greater in eyes with SDDs compared with those without (Table 3). The choroid was significantly ($P < 0.001$) thinner in subjects with SDDs compared with those without SDDs (Table 3). There was no meaningful correlation between drusen volume, GA area, and choroidal thickness measurements in eyes with SDDs (Table 4), although there was a weak correlation between choroidal thickness and GA area. Interestingly, however, a statistically significant correlation ($r = 0.45$, $P < 0.001$) was observed between drusen volume and GA area in eyes without SDDs.

Discussion

We describe the SD-OCT characteristics of AMD in an elderly Amish population that has not been reported previously. We have qualitatively characterized AMD features beyond automated quantitative measures on SD-OCT. Rather than analyzing a single scan, we have reviewed all B-scans in the macular cubes. This provides a complete survey of the morphological characteristics on SD-OCT and their prevalence in this population.

The qualitative analysis of AMD features from SDOCT imaging as described in Table 1 was guided by previous studies on AMD.^{5,24–26} Using the high-resolution cross-sectional SD-OCT scans, we were able to identify intra- or subretinal fluid, subretinal tissue, outer retinal

tubulation, SDDs, intraretinal HRF (including their axial extent), and pigment epithelial detachment. Outer retinal tubulations are branching tubular structures in the outer nuclear layer seen on *en face* OCT scans that appear as round or ovoid hyporeflective spaces with hyperreflective borders on OCT B-scans (Figure 2A). Twenty-seven eyes (1.2%) in this study had outer retinal tubulations, which have been associated with a slower growth rate of GA lesions.³³ In future analyses, it will be interesting to explore the heritability of these lesions.

Previous reports have found that the presence of HRF over drusen portends a high risk for the development and progression of GA over time.²⁵ Hyperreflective foci are believed to represent the migration of RPE cells into the neurosensory retina.^{25,34} In this study, 18% of subjects with AMD had HRF. In previous reports,²⁵ the innermost extent of the HRF within the retina was not a significant independent risk factor for developing GA. However, because the HRF may migrate internally over time, the extent of migration may reflect the time since the initial migration event. In the present study, the HRF were found to extend as far as the outer plexiform layer in 26% of eyes.

Previous publications on OCT-based automated quantification of drusen parameters have shown the accuracy and reproducibility of the automated algorithm for detecting and measuring drusen area, volume, and GA area.^{14,35–37} In this study, we have used the algorithm to analyze and study drusen characteristics in elderly Amish patients. Traditionally, drusen quantification has been performed by color imaging methods, but there is imprecision with respect to measuring drusen area or size, a known indicator of AMD progression.^{16,38,39} Similar to previous studies,^{24,40} our study showed comparable drusen measurements between both eyes of subjects, with a significant correlation for drusen area and volume. In this report, we are describing only drusen metrics at a specific point in time. It is our intent in the future to remeasure drusen metrics in this population to calculate drusen growth and turnover rate. These end points could be useful for genetic association studies or targets for therapeutics.

Subretinal drusenoid deposits are a distinct OCT feature found in many diseases,⁴¹ including AMD, which appear to correspond to reticular pseudodrusen (RPD) lesions evident on IR or blue-light FAF imaging.^{42,43} Our results do confirm the superiority of SDOCT, IR, and FAF over color fundus photography (CFP) for detection of SDD and RPD. Analysis of our CFP for RPD/SDD on 2,191 eyes showed a detection rate of only 1.5% (34 eyes). We also found an increased sensitivity to detect these lesions with IR/ FAF compared with SD-OCT (7% vs. 3.1%). This difference could be partially explained by the fact that many of these SDD lesions may be located outside the field of view of the obtained OCT scans.⁴⁴ This is perhaps not surprising because SDDs are known to have a higher prevalence along the outer border of the macula, whereas regular drusen tend to accumulate more centrally. Hopefully, with faster OCT devices in the future (e.g., swept-source OCT), larger areas can be scanned easily, improving the detection sensitivity of OCT for these lesions. Regardless, our observed OCT prevalence rates have merit because they reflect the current commonly obtained scan patterns in practice.

Previous studies estimating the prevalence of SDDs have used varying inclusion criteria, case definitions, and imaging modalities. The Beaver Dam and Blue Mountains Eye Studies both evaluated eyes (albeit using different metrics) for SDDs from color fundus photographs (CFP) and reported SDD prevalences of 0.7% and 1.95%, respectively.^{45,46} Recently, Zarubina et al⁴⁷ compared their SDD prevalence in the AL-STAR cohort based on CFPs to the Beaver Dam and Blue Mountain study using the same metrics and found a prevalence of 1.48% and 1.97%, respectively. Our prevalence in the Amish cohort using CFPs was 1.5%. Our prevalence of SDDs increased to 7.0% when including the results of multimodal imaging. Still, this prevalence is lower than the reported prevalence (32%) in the ALSTAR cohort.⁴⁷ We considered five possible explanations for this different result: 1) the ALSTAR cohort evaluated the peripapillary area more extensively than our study. Of note is their finding that 47% of persons with SDDs were detected exclusively on the optic nerve head SD-OCT; 2) the Amish cohort is twice the size of the ALSTAR cohort, making it less prone to statistical errors; 3) the AL-STAR cohort is a clinic-based sample recruited from two primary care ophthalmology practices at a major teaching hospital, whereas the Amish cohort was more population based although more focused on families; 4) the Amish cohort was younger than the ALSTAR cohort (mean age = 65 years vs. 69 years); 5) the ALSTAR cohort is mostly white and some are non-whites, whereas our cohort is selected for the Amish; and 6) the Amish do not smoke, whereas 46% of the ALSTAR participants were either former/current smokers.

Careful analysis of previous studies reporting SDD prevalence requires rigorous interpretation. For example, reports assessing only AMD subjects with SD-OCT and IR have reported a prevalence as high as 58%,⁴⁸ whereas studies using SD-OCT, IR, and FAF have reported estimates as high as 69% and as low as 18%.⁴⁹ These estimates can vary with different study population samples and imaging techniques and may not reflect the population rates. Interestingly, we found SDDs in eight individuals (11 eyes) who had no evidence of drusen or pigment alterations suggestive of AMD. One limitation to our study is that it is a cross-sectional assessment. Subretinal drusenoid deposits have been shown^{28,41} to evolve over time requiring a progression study to assess their overall progression with the AMD disease process.

Arnold et al⁵⁰ found a marked decrease in choroidal thickness in subjects with SDDs. Similarly, we found a significantly thinner choroid in eyes with SDDs. It has been suggested that choroidal thinning may have occurred because of the fibrotic replacement of the middle layer of the choroid.⁵⁰ Studies⁴⁴ have shown a high prevalence of late AMD among patients with SDDs. We also found that drusen volume and GA area were significantly higher in subjects with SDDs compared with those without SDDs.

In summary, we have described SD-OCT parameters in an elderly Amish population with AMD. We have observed that SDDs can be found in the absence of other AMD features and may influence the thickness of the choroid.

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Fig. 1. Cirrus-automated RPE analysis algorithm providing quantitative measures of drusen area, volume in center 3 mm and 5 mm circular zones, and GA area in central 5 mm zone. **A.** Infrared image with RPE thickness profile, drusen map, **(B)** quantitative measures generated by the automated algorithm, and **(C)** OCT B-scan with automated software-segmented boundaries.

Fig. 2. Spectral domain optical coherence tomography **B**-scan showing (white arrow) outer retinal tubulation (**A**) and HRF over drusen (**B**).

Fig. 3. Illustration of subretinal drusenoid deposits (SDDs) on infrared reflectance (IR) and OCT images. The OCT-scanned regions are outlined in light grey boxes on the IR images (A). The horizontal grey lines, indicated by white arrows, denote the locations of selected B-scans (B,C). The black arrows on the OCT B-scans identify individual SDD lesions.

Fig. 4. Bland–Altman plots demonstrating intra-(**A**) and intergrader (**B**) reproducibility of subfoveal choroidal thickness. Dashed lines: 95% limits of agreement.

Table 1.

Frequencies of Spectral Domain Optical Coherence Tomography Findings in an Elderly Amish Population

SD-OCT Parameter N = 2,191 Eyes	Present in n (%)
Subretinal fluid *	30 (1.4)
Subretinal hyperreflective material *	30 (1.4)
Intraretinal cysts *	78 (3.9)
Outer retinal tubules *	27 (1.2)
Subretinal drusen *	68 (3.1)
Geographic atrophy †	99 (4.5)
Hyperreflective foci over drusen *	167 (7.6)
Hyperreflective foci extent (n = 190 eyes)	
Photoreceptor cell layer	12 (7.2)
Outer nuclear layer	112 (67.1)
Outer plexiform layer	43 (25.7)
Pigment epithelial detachment *	
Drusenoid	324 (14.8)
Fibrovascular	30 (1.4)
Serous	11 (0.5)

* Cirrus-derived thickness values.

† Spectralis-derived thickness values.

Table 2.
Descriptive Details of Quantitative Study Parameters in an Age-Related Macular Degeneration Cohort of the Study

Variable	All Eyes n = 1,009 Eyes (Mean ± SD; Range)	Right Eyes n = 499 Eyes (Mean ± SD; Range)	Left Eyes n = 510 Eyes (Mean ± SD; Range)	Intraclass Correlation in Sibpairs			Correlation of all Subjects		
				Pair Cnt	Eqv Pair Cnt	r ± SE (P)	Pair Cnt	Eqv Pair Cnt	r ± SE (P)
Drusen area in 3 mm [*]	0.22 ± 0.68 (0–6.7)	0.20 ± 0.64 (0–6.4)	0.23 ± 0.73 (0–6.7)	358	144.3	0.0507 ± 0.0833 (0.5464)	413	171.5	0.5429 ± 0.0544 (<0.0001)
Drusen area in 5 mm [*]	0.39 ± 1.25 (0–13.3)	0.37 ± 1.25 (0–13.3)	0.41 ± 1.21 (0–12.7)	355	80.7	0.0846 ± 0.1078 (0.4403)	412	121.4	0.7325 ± 0.0433 (<0.0001)
Drusen volume in 3 mm [*]	0.01 ± 0.08 (0–1.63)	0.01 ± 0.08 (0–1.63)	0.02 ± 0.09 (0–1.04)	358	110.7	0.0255 ± 0.0945 (0.7912)	413	109.8	0.3616 ± 0.0837 (<0.0001)
Drusen volume in 5 mm [*]	0.02 ± 0.12 (0–2.19)	0.02 ± 0.12 (0–2.19)	0.03 ± 0.11 (0–1.5)	358	85.6	0.0438 ± 0.1085 (0.6906)	413	93.9	0.5021 ± 0.0783 (<0.0001)
GA area 5 mm [*]	0.47 ± 2.30 (0–19.1)	0.49 ± 2.37 (0–19.1)	0.45 ± 2.22 (0–19.1)	362	78.3	0.0413 ± 0.1135 (0.7196)	415	427.1	0.8451 ± 0.0141 (<0.0001)
Cirrus-choroidal thickness [†]	246 ± 75 (23–439)	247 ± 75 (26–439)	245 ± 76 (23–432)	333	165.1	0.2881 ± 0.0717 (0.0002)	380	395.8	0.8398 ± 0.0151 (<0.0001)
Spectrals-choroidal thickness [‡]	244 ± 78 (23–478)	245 ± 78 (23–478)	243 ± 77 (23–428)	336	168.4	0.2778 ± 0.0714 (0.0002)	404	483.1	0.8279 ± 0.0145 (<0.0001)

n-overall sample (eye) count, note that the actual sample size is slightly smaller because of missing values.

^{*} From the center of fovea.

[†] Cirrus-derived thickness values.

[‡] Spectrals-derived thickness values.

Eqv Pair Cnt, equivalent pair count; r, correlation between the right and left eye.

Table 3.

Quantitative Measures in Subjects With and Without SDD/RPD

Variable	No RPD Cohort, n = 2,046 Eyes (Mean $\pm$ SD; Range)	RPD Cohort, n = 143 Eyes (Mean $\pm$ SD; Range)	P
Drusen area in 5 mm [*]	0.14 $\pm$ 0.73 (0–13.3)	1.22 $\pm$ 2.06 (0–12.8)	<0.001
Drusen volume in 5 mm [*]	0.01 $\pm$ 0.05 (0–1.00)	0.08 $\pm$ 0.25 (0–2.19)	<0.001
GA area 5 mm [*]	0.15 $\pm$ 1.41 (0–19.1)	1.55 $\pm$ 3.70 (0–19.1)	<0.001
Spectrals-choroidal thickness [†]	259 $\pm$ 69 (23–488)	172 $\pm$ 82 (31–367)	<0.001

n-overall sample (eye) count, note that the actual sample size is slightly smaller because of missing values.

^{*} From the center of fovea.[†] Spectrals-derived thickness values.

RPD, reticular pseudodrusen.

Table 4.

Correlations Between Study Parameters in Subjects With and Without SDD/RPD

Variable 1	Variable 2	r ± SE	P	Pair Cnt	Eqv Pair Cnt
SDD cohort					
Drusen volume	GA area	0.1746 ± 0.1581	0.2913	60	38.8
Drusen volume	Choroidal thickness	−0.0704 ± 0.1865	0.7168	54	29.5
Choroidal thickness	GA area	−0.2066 ± 0.1847	0.2936	53	28.1
No SDD cohort					
Drusen volume	GA area	0.4507 ± 0.0279	<0.0001	986	815.4
Drusen volume	Choroidal thickness	−0.1962 ± 0.0382	<0.0000	918	635.9
Choroidal thickness	GA area	−0.1315 ± 0.0391	<0.0001	920	632.4

r, correlation; Eqv Pair Cnt, equivalent pair count.