Published in final edited form as:

Retina. 2017 October ; 37(10): 1880–1887. doi:10.1097/IAE.0000000000001428.

Association of Drusen Volume with Choroidal Parameters in Non-Neovascular Age-Related Macular Degeneration

Siva Balasubramanian, MD, PhD^{1,2}, Jianqin Lei, MD^{1,2,3}, Muneeswar G. Nittala, Mphil^{1,2}, Swetha B. Velaga BS^{1,2}, Jonathan Haines, PhD⁴, Margaret A. Pericak-Vance, PhD⁵, Dwight Stambolian, MD, PhD⁶, and SriniVas R. Sadda, MD^{1,2}

¹Doheny Image Reading Center, Doheny Eye Institute, Los Angeles, CA

²Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, CA

³1st affiliated hospital of Xi'an Jiaotong university, Xi'an, China

⁴Department of Epidemiology & Biostatistics, Case Western Reserve University, Cleveland, Ohio

⁵John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida

⁶Department of Ophthalmology, University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania

Abstract

Purpose—The choroid is thought to be relevant to the pathogenesis of non-neovascular age-related macular degeneration (NNVAMD), but its role has not yet been fully defined. In this study, we evaluate the relationship between the extent of macular drusen and specific choroidal parameters, including thickness and intensity.

Methods—Spectral-domain optical coherence tomography (SD-OCT) images were collected from two distinct, independent cohorts with NNVAMD: Amish (53 eyes of 34 subjects) and non-Amish (40 eyes from 26 subjects). All SD-OCT scans were obtained using the Cirrus HD-OCT with a 512×128 macular cube (6x6mm) protocol. The Cirrus advanced RPE analysis tool was used to automatically compute drusen volume within 3 mm (DV3) and 5 mm (DV5) circles centered on the fovea. The inner and outer borders of the choroid were manually segmented and the mean choroidal thickness (CT) and choroidal intensity (CI; i.e. brightness) were calculated. The CI was normalized against the vitreous and nerve fiber layer reflectivity. The correlation between DV and these choroidal parameters was assessed using Pearson and linear regression analysis.

Results—A significant positive correlation was observed between normalized choroidal intensity (NCI) and DV5 in the Amish ($r = 0.42$, $p = 0.002$) and non-Amish ($r = 0.33$, $p = 0.03$) cohorts. Also, DV3 showed a significant positive correlation with NCI in both the groups (Amish: $r = 0.30$, $p = 0.02$; non-Amish: $r = 0.32$, $p = 0.04$). Choroidal thickness was negatively correlated to NCI in

both Amish ($r = -0.71$, $p = 0.001$) and non-Amish ($r = -0.43$, $p = 0.01$) groups. NCI was the most significant constant predictor of DV in both the Amish and non-Amish.

Conclusions—Choroidal intensity, but not choroidal thickness, appears to be associated with drusen volume in Amish and non-Amish populations. These observations suggest that choroidal parameters beyond thickness warrant further study in the setting of AMD.

Keywords

Age-related macular degeneration; SD-OCT; drusen volume; choroidal intensity; choroidal thickness

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among people aged 50 years or older in the developed world.¹ AMD is an incompletely understood complex multifactorial disease influenced by genetic, environmental, metabolic, and functional factors.² Vision loss due to AMD is expected to increase substantially in the future years with the rapidly growing aging population. In the United States alone, the number of people suffering from advanced AMD is projected to reach three million by the year 2020.³

Drusen are considered to be the hallmark clinical sign of non-neovascular AMD (NNVAMD) and quantity of drusen area is known to be an important risk factor for progression to advanced AMD, manifest as geographic atrophy (GA) or choroidal neovascularization (CNV).^{4,5} Typical drusen associated with AMD are thought to be focal extracellular deposits of proteins and lipids at level of Bruch's membrane (BrM) situated between the retinal pigment epithelium (RPE) and the choriocapillaris.⁶ Drusen appear yellowish on clinical examination and by traditional flash color fundus photography. The borders of drusen can often be poorly-demarcated ("soft" or "indistinct") which can present a challenge for quantification. Historical methods for quantifying drusen area on color photographs have been qualitative or semi-quantitative, and largely based on determining the level of drusen in an eye compared to standardized circles of known area. Drusen, however, are well-seen on spectral-domain OCT, and the three-dimensional information allows drusen volume (DV) rather than just drusen area to be quantified. Automated algorithms for quantification of DV are commercially available and have been shown to be highly reproducible.⁷ We have also demonstrated that these algorithms can be highly accurate when compared to manual segmentation by human graders.⁸ We also observed that OCT-derived DV was an important risk factor for progression to advanced AMD.⁹ In addition, in an elderly Amish population, we demonstrated that DV could be a potentially useful endophenotype for genetic studies.¹⁰

The choroid is a major vascular layer of the eye, and is critical for providing metabolic support to the RPE and photoreceptors.¹¹ The choroid itself is commonly divided into three vascular layers, consisting of an inner sinusoidal capillary network (choriocapillaries), a middle layer of medium-sized vessels (Sattler's layer) and an outer layer composed of larger vessels (Haller's layer).¹² Several studies have investigated the role of choroid in the

pathogenesis of AMD,¹³ and changes in choroidal thickness (CT) have been suggested as an indicator of ocular¹⁴ and systemic health.¹⁵ Recently, in an elderly Amish population, we were able to demonstrate that CT may also be heritable.¹⁰ Thickness alone, however, may not be the only choroidal parameter of interest. The reflectivity or brightness of the choroid may also be altered by disease.

The association between choroidal parameters and DV, however, has not been well-defined. In this study, we evaluate the relationship between DV and CT and reflectivity in our elderly Amish patients with NNVAMD, and compare these findings with a non-Amish AMD cohort.

Methods

The study was approved by the Institutional Review Boards of the University of California Los Angeles, the University of Miami and the University of Pennsylvania. All procedures were conducted in accordance with the 2000 Declaration of Helsinki. Written informed consent was obtained from each subject prior to being enrolled in the study. The data from the Amish subjects was obtained from an ongoing study at the University of Pennsylvania and the University of Miami aimed at better understanding the genetics of AMD in this population. The non-Amish subjects were recruited from the Medical Retina Clinics of the Doheny-UCLA Eye Centers.

Subjects

The demographic profile of the study groups with early or intermediate NNVAMD are illustrated in Table 1. NNVAMD was classified based on Age Related Eye Diseases Study (AREDS) classification: AREDS category 2 (numerous small drusen or a few medium drusen) and AREDS category 3 (numerous medium or at least one large drusen).¹⁶ All subjects underwent a complete ophthalmic examination including color fundus photograph and SD-OCT imaging.

Exclusion criteria for the study were poor OCT image quality (signal strength < 6) due to significant media opacity, GA, CNV, optic nerve pathologies or evidence of other retinal disease.

SD-OCT image acquisition and Drusen Volume Calculation

All subjects underwent SD-OCT (Cirrus OCT, Carl Zeiss Meditec, Dublin, CA) imaging using a 6x6mm macular cube protocol (128 B-scans and 512 A-scans per B-scan) centered on the fovea. The Cirrus Advanced RPE Analysis tool was used to automatically quantify drusen volume (DV) within circles of 3mm (DV3) and 5 mm (DV5) diameter. The segmented B-scans were reviewed for segmentation errors and manually corrected if needed.

Choroidal Parameter Generation

Raw OCT data obtained from SD-OCT were uploaded into the previously described and validated grading software, the 3D-OCTOR (Doheny Eye Institute, Los Angeles, CA).^{17,18} 3D-OCTOR allows the user to manually define and segment various retinal boundaries in

SD-OCT B-scans. After segmenting or defining the retinal layers of interest, the software computes mean thickness and intensity of the segmented layers from the scan pixel measurements.

A total of five layers were segmented from the foveal center subfield B-scans (Figure 1): (1) vitreous (2) ILM (3) NFL (4) inner border of choroid and (5) outer border of choroid, according to the Doheny Image Reading Center protocol described previously.^{8,19} The grading procedure was carried out by two trained, certified, independent graders (SB & SBV) who were masked to the group assignment or the drusen volume measurements. In situations of disagreement between gradings, the cases were adjudicated by the Doheny Image Reading Center medical director (SS) to yield a single final grading result for each case for use in subsequent analysis. Although previously established,²⁰ the inter-grader reproducibility of the results of manual segmentation were also evaluated in this study.

Following manual segmentation, the mean thickness of the choroid in the foveal center subfield was computed. The 3D-OCTOR also allows calculation of the mean intensity or brightness [optical density (OD)] of the choroid by averaging all pixels contained between its inner and outer boundaries.

Normalization of choroidal intensity (CI)

During image acquisition, several factors such as media opacity and scan tilt may affect signal quality and brightness of the structures visualized by SD-OCT. Normalization is a method to estimate the absolute brightness or intensity of the tissue/s. Previous reports have described methods to normalize signal intensities between subject visits.^{21,22} The normalization approach we followed involves the use of a dark structure, the vitreous and a bright structure, the nerve fiber layer, as reference standards. These two structures are relatively unaffected by the AMD pathology, and considered to be the ideal reference standards.¹⁹ Another bright structure on OCT is the RPE, but this layer is not ideally suited for use in normalization as it may be involved by the AMD disease process.

Similar to our previous studies,²³ in this analysis, CI was normalized by subtracting the mean vitreous brightness/intensity (VI) from mean un-normalized CI, and the remainder was divided by the mean brightness/intensity of the NFL (NFL intensity). The resultant normalized intensity value for the pixels in the choroid are unit-less. The value is generally less than one since the NFL tends to be one of the brightest structures in the image. The formula for normalizing choroidal intensity is as follows:

$$\text{Normalized choroidal intensity (NCI)} = \frac{CI - VI}{\text{NFL intensity}}$$

Statistical analysis

The results obtained were expressed as mean $\pm$ standard deviation. The correlation between DV, age and the choroidal parameters were assessed using bivariate Pearson correlation. Linear regression analysis was used to predict the relationship between DV (as dependent variable), and age and choroidal parameters (as independent variables). The inter-grader

segmentation reproducibility was assessed using intraclass correlation coefficient. All the statistical analysis were performed using IBM® SPSS® software, version 20, and a p -value of <0.05 was considered significant.

Results

The Amish group (53 eyes from 34 subjects) and the non-Amish group had a mean age of 74.48 ± 9.11 years and 74.39 ± 6.52 years respectively (Table 1). Among the study eyes, 66% (Amish) and 72.5% (non-Amish) were from women. The differences in age, DV3, DV5, NCI and CT were not statistically significant between the groups (Table 2). Significant positive correlations were found between NCI and DV3 ($r = 0.32$, $p = 0.02$), DV5 ($r = 0.42$, $p = 0.002$) in the Amish population (Figure 2). The NCI was also positively correlated to DV3 ($r = 0.33$, $p = 0.04$) and DV5 ($r = 0.33$, $p = 0.03$) among the non-Amish cohort (Figure 3). The negative correlations between NCI and CT were significant in Amish ($r = -0.71$, $p = 0.001$) (Figure 4) and non-Amish groups ($r = -0.43$, $p = 0.01$) (Figure 5). Correlations were not significant in both the groups when DV3 or DV5 was compared with age or CT (Table 3). CT and NCI were not correlated with age in both Amish and non-Amish (Table 3).

Linear regression model analysis showed NCI as the most significant constant predictor of DV (Table 4). Two graders had an intraclass correlation coefficient of 0.95 (95% confidence interval [CI]: 0.86–0.98) in measuring CT, and 0.94 (95% CI: 0.84–0.98) for computing NCI.

Discussion

The relationship between drusen and choroid in the pathogenesis of NNVAMD has been a topic of considerable discussion and speculation over many years. To our knowledge, this study for the first time has examined the relationship between SD-OCT generated DV and choroidal parameters in two distinct groups, Amish and non-Amish population. In particular, the role of NCI had not been evaluated in early or NNVAMD. We included two study population, Amish and non-Amish in order to ascertain the phenotypic similarities or differences in DV and choroid between these two groups.

In this study of elderly Amish and non-Amish individuals with early or intermediate AMD, NCI was positively correlated with DV and negatively associated with CT. Interestingly, CT, which is correlated with AMD and the development of CNV and GA, did not show any relationship with DV. Of note, we also failed to observe a relationship between CT and age in our cohorts. Our findings are consistent with previous reports showing that CT may not be affected by age in early AMD.^{24–26} Although, studies have demonstrated that the choroid appears to measure thinner with advancing age,^{27–29} age-related choroidal thinning was particularly prevalent in those with advanced AMD.^{26,30,31}

Our Amish and non-Amish cohorts were quite similar with regards to various parameters, including age, choroidal thickness, and DV within the central 3mm and 5 mm circle in SD-OCT. The parameters in our study also correlate well with the previously reported histopathologic studies in AMD donor eyes,^{32,31,33} but the histopathologic basis of the higher NCI is not entirely clear.

The mean choroidal intensity is a reflection of both the choroidal vessels and the surrounding stromal tissue. Assuming that the vessels maintain a similar darkness, an increase in NCI could be the result of a reduction in choroidal vessels (i.e. an increase in stroma/vessels ratio), an increase in the reflectivity of the stroma itself, or both. We do know that the density of the choroidal vasculature is significantly reduced in AMD eyes compared to non AMD,³² and that choroidal thinning occurs with accentuation of the larger choroidal vessels in eyes with AMD.³¹ But there are also conflicting reports showing no difference in CT among normal and different stages of AMD.³² DV was associated with NCI but not correlated to CT in this study, therefore the intrinsic choroidal alterations might commence during the early stages of AMD before apparent choroidal thinning. However, differentiating amongst these possible explanations for a higher NCI will require additional analyzes to extract the choroidal vasculature and compute the reflectivity of the choroidal stroma alone. Although some groups have demonstrated extraction of choroidal vasculature from the intensity images in non-AMD settings,^{34,35} this is a difficult task to do reliably. It is possible that advances in OCT angiography may eventually aid in this task.

It should be noted, however, that the apparent differences in NCI between individuals may have nothing to do with intrinsic choroidal alterations. It is possible that depigmentation of the RPE or subtle thinning of the retina in these early/intermediate AMD eyes may have led to an overall brighter choroid in these eyes with more drusen. Regardless of the precise explanation, however, given its relevance to overall drusen burden, NCI would seem to be a parameter worthy of further study.

Our study is not without limitations, most notable is not having the axial length or refractive error information for the two different populations. As a result we were unable to further adjust or correct our CT values based on the axial length. To our knowledge, however, this should not have an impact on choroidal reflectivity. On other hand, the inclusion of two separate and independent populations (a non-Amish cohort to compare to our existing Amish cohort) gives greater strength and confidence in our observation that NCI appears to be associated with DV. Our study also has several other strengths including the use of certified reading center graders and inclusion of two independent cohorts.

In summary, among the two separate cohorts of subjects with early or intermediate AMD, we observed that a higher NCI was significantly correlated with a higher volume of drusen in the macula. Choroidal intensity would appear to be a parameter that warrants further evaluation in future prospective studies. Validation of our results using swept source OCT or OCT angiography will be essential to establish the clinical relevance of choroidal intensity in AMD.

Acknowledgments

Funding Support: Supported by the National Eye Institute, Bethesda, Maryland (grant #RO1 EY023164-03) and the Department of Ophthalmology at the Perelman School of Medicine, Univ. of Pennsylvania, Philadelphia, Pennsylvania. Funds also were received from the Macular Vision Research Foundation and F.M. Kirby Foundation. Dr. Sadda is a consultant for Carl Zeiss Meditec, Optos, Allergan, Genentech, Alcon, Novartis and Roche. He receives research funding from Carl Zeiss Meditec, Optos, Allergan and Genentech. He also receives honoraria from Carl Zeiss Meditec, Optos and Allergan. Other authors have no financial interest to declare, and no conflicting relationship exists for any author.

References

1. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol*. 2012; 96(5):614–618. DOI: 10.1136/bjophthalmol-2011-300539 [PubMed: 22133988]
2. Nowak JZ. Age-related macular degeneration (AMD): pathogenesis and therapy. *Pharmacol Rep*. 2006; 58(3):353–363. [PubMed: 16845209]
3. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004; 122(4):564–572. DOI: 10.1001/archophth.122.4.564 [PubMed: 15078675]
4. Khanifar AA, Koreishi AF, Izatt JA, Toth CA. Drusen ultrastructure imaging with spectral domain optical coherence tomography in age-related macular degeneration. *Ophthalmology*. 2008; 115(11):1883–1890. [PubMed: 18722666]
5. Hageman GS, Luthert PJ, Victor Chong NH, Johnson LV, Anderson DH, Mullins RF. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retin Eye Res*. 2001; 20(6):705–732. DOI: 10.1016/S1350-9462(01)00010-6 [PubMed: 11587915]
6. Crabb JW, Miyagi M, Gu X, et al. Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2002; 99(23):14682–14687. DOI: 10.1073/pnas.222551899 [PubMed: 12391305]
7. Gregori G, Wang F, Rosenfeld PJ, et al. Spectral domain optical coherence tomography imaging of drusen in nonexudative age-related macular degeneration. *Ophthalmology*. 2011; 118(7):1373–1379. DOI: 10.1016/j.ophtha.2010.11.013 [PubMed: 21388687]
8. Nittala MG, Ruiz-Garcia H, Sadda SR. Accuracy and reproducibility of automated drusen segmentation in eyes with non-neovascular age-related macular degeneration. *Investig Ophthalmol Vis Sci*. 2012; 53(13):8319–8324. DOI: 10.1167/iops.12-10582 [PubMed: 23150629]
9. Abdelfattah NS, Zhang H, Boyer DS, et al. Drusen volume as a predictor of disease progression in patients with late age-related macular degeneration in the fellow eye. *Investig Ophthalmol Vis Sci*. 2016; 57(4):1839–1846. DOI: 10.1167/iops.15-18572 [PubMed: 27082298]
10. Chavali V, Diniz B, Huang J, Ying GS, Sadda S, Stambolian D. Association of OCT-Derived Drusen Measurements with AMD-Associated Genotypic SNPs in the Amish Population. *J Clin Med*. 2015; 4(2):304–317. DOI: 10.3390/jcm4020304 [PubMed: 25893111]
11. Kur J, Newman EA, Chan-Ling T. Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease. *Prog Retin Eye Res*. 2012; 31(5):377–406. DOI: 10.1016/j.preteyeres.2012.04.004 [PubMed: 22580107]
12. Esmaeelpour M, Kajic V, Zabihiyan B, et al. Choroidal Haller's and Sattler's layer thickness measurement using 3-dimensional 1060-nm optical coherence tomography. *PLoS One*. 2014; 9(6):doi: 10.1371/journal.pone.0099690
13. Koizumi H, Yamagishi T, Yamazaki T, Kawasaki R, Kinoshita S. Subfoveal choroidal thickness in typical age-related macular degeneration and polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol*. 2011; 249(8):1123–1128. DOI: 10.1007/s00417-011-1620-1 [PubMed: 21274555]
14. Lindner M, Bezatis A, Czauderna J, et al. Choroidal thickness in geographic atrophy secondary to age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2015; 56(2):875–882. DOI: 10.1167/iops.14-14933 [PubMed: 25587059]
15. Vujosevic S, Martini F, Cavarzeran F, Pilotto E, Midena E. Macular and Peripapillary Choroidal Thickness in Diabetic Patients. *Retina*. 2012; 32(October 2012):1.doi: 10.1097/IAE.0b013e31825db73d
16. Ferris FL, Davis MD, Clemons TE, et al. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol*. 2005; 123(18):1570–1574. DOI: 10.1016/S0084-392X(08)70302-2 [PubMed: 16286620]
17. Sadda SR, Keane PA, Ouyang Y, Updike JF, Walsh AC. Impact of scanning density on measurements from spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2010; 51(2):1071–1078. DOI: 10.1167/iops.09-4325 [PubMed: 19797199]

18. Sadda SR, Joeres S, Wu Z, et al. Error correction and quantitative subanalysis of optical coherence tomography data using computer-assisted grading. *Invest Ophthalmol Vis Sci.* 2007; 48(2):839–848. DOI: 10.1167/iops.06-0554 [PubMed: 17251486]
19. Charafeddin W, Nittala MG, Oregon A, Sadda SR. Relationship between subretinal hyperreflective material reflectivity and volume in patients with neovascular age-related macular degeneration following anti-vascular endothelial growth factor treatment. *Ophthalmic Surg Lasers Imaging Retin.* 2015; 46(5):523–530. DOI: 10.3928/23258160-20150521-03
20. Joeres S, Tsong JW, Updike PG, et al. Reproducibility of quantitative optical coherence tomography subanalysis in neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2007; 48(9):4300–4307. DOI: 10.1167/iops.07-0179 [PubMed: 17724220]
21. Lee SY, Stetson PF, Ruiz-Garcia H, Heussen FM, Sadda SR. Automated characterization of pigment epithelial detachment by optical coherence tomography. *Investig Ophthalmol Vis Sci.* 2012; 53(1):164–170. DOI: 10.1167/iops.11-8188 [PubMed: 22159019]
22. Hu Z, Nittala MG, Sadda SR. Comparison of Retinal Layer Intensity Profiles From Different OCT Devices. *Ophthalmic Surg Lasers Imaging Retina.* 2013; 44(6 Suppl):S5–S10. DOI: 10.3928/23258160-20131101-02 [PubMed: 24220885]
23. Charafeddin W, Nittala MG, Oregon A, Sadda SR. Relationship between subretinal hyperreflective material reflectivity and volume in patients with neovascular age-related macular degeneration following anti-vascular endothelial growth factor treatment. *Ophthalmic Surg Lasers Imaging Retin.* 2015; 46(5):523–530. DOI: 10.3928/23258160-20150521-03
24. Wood A, Binns A, Margrain T, et al. Retinal and choroidal thickness in early age-related macular degeneration. *Am J Ophthalmol.* 2011; 152(6)doi: 10.1016/j.ajo.2011.05.021
25. Ramrattan RS, Van der Schaft TL, Mooy CM, De Bruijn WC, Mulder PGH, De Jong PTVM. Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. *Investig Ophthalmol Vis Sci.* 1994; 35(6):2857–2864. [PubMed: 8188481]
26. Chung SE, Kang SW, Lee JH, Kim YT. Choroidal thickness in polypoidal choroidal vasculopathy and exudative age-related macular degeneration. *Ophthalmology.* 2011; 118(5):840–845. DOI: 10.1016/j.ophtha.2010.09.012 [PubMed: 21211846]
27. Manjunath V, Taha M, Fujimoto JG, Duker JS. Choroidal thickness in normal eyes measured using cirrus HD optical coherence tomography. *Am J Ophthalmol.* 2010; 150(3)doi: 10.1016/j.ajo.2010.04.018
28. Abbey AM, Kuriyan AE, Modi YS, et al. Optical coherence tomography measurements of choroidal thickness in healthy eyes: correlation with age and axial length. *Ophthalmic Surg Lasers Imaging Retina.* 2015; 46(1):18–24. DOI: 10.3928/23258160-20150101-03 [PubMed: 25559504]
29. Yiu G, Chiu SJ, Petrou PA, et al. Relationship of Central Choroidal Thickness with Age-Related Macular Degeneration Status. *Am J Ophthalmol.* 2015; 159(4):617–626. DOI: 10.1016/j.ajo.2014.12.010 [PubMed: 25526948]
30. Mcleod DS, Grebe R, Bhutto I, Merges C, Baba T, Luttu GA. Relationship between RPE and choriocapillaris in age-related macular degeneration. *Investig Ophthalmol Vis Sci.* 2009; 50(10): 4982–4991. DOI: 10.1167/iops.09-3639 [PubMed: 19357355]
31. van Driel D, Sarks SH. Ageing and degeneration in the macular region of the eye. *Micron* (1969). 1980; 11(3-4):451–452. DOI: 10.1016/0047-7206(80)90091-6
32. Spraul CW, Lang GE, Grossniklaus HE, Lang GK. Histologic and Morphometric Analysis of the Choroid, BrM and RPE in Postmortem Eyes With AMD and Histologic Examination of Surgically Excised CNV Membranes. *Surv Ophthalmol.* 1999; 44(1):10–32. DOI: 10.1016/S0039-6257(99)00086-7.
33. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res.* 2010; 29(2):144–168. DOI: 10.1016/j.preteyeres.2009.12.002 [PubMed: 20044062]
34. Agrawal R, Salman M, Tan KA, et al. Choroidal vascularity index (CVI) - A novel optical coherence tomography parameter for monitoring patients with panuveitis? *PLoS One.* 2016; 11(1)doi: 10.1371/journal.pone.0146344
35. Agrawal R, Chhablani J, Tan KA, Shah S, Sarvaiya C, Banker A. Choroidal Vascularity Index in Central Serous Chorioretinopathy. *Retina.* 2016; :1–6. DOI: 10.1097/IAE.0000000000001040

Summary Statement

We evaluated two separate cohorts (Amish and non-Amish) with early or intermediate AMD using a novel technique, and we observed that increase in choroidal intensity was significantly correlated with a higher volume of drusen in the macula. Choroidal intensity would appear to be a parameter that warrants further study in future prospective studies.

Figure 1. SD-OCT B-scan of the right eye in a patient with NNVAMD. (A) Raw unsegmented OCT B-scan image generated by Cirrus™ HD-OCT. (B) OCT B-scan image following manual segmentation of (1) vitreous (2) ILM (3) NFL (4) inner border of choroid and (5) outer border of choroid, using 3D-OCTOR.

Figure 2.

Correlation analysis between normalized choroidal intensity (NCI) in the X-axis and drusen volume (DV) in the Y-axis among the Amish population.

Figure 3.
Positive correlation between normalized choroidal intensity (NCI) and drusen volume (DV) in non-Amish.

Figure 4.

Negative correlation between choroidal thickness (CT) in X-axis and drusen volume (DV) in the Y-axis among the Amish and non-Amish cohort.

Table 1

Demographics of the study.

Groups	Amish	Non-Amish
Total subjects	34	26
Total eyes	53	40
Men	18	11
Women	35	29
Age (years)	72.09 $\pm$ 8.82	74.40 $\pm$ 6.37

Age is expressed as mean $\pm$ standard deviation

Table 2

Age, DV and choroidal parameters (NCI and CT) comparison between Amish and non-Amish groups.

Groups	Amish	Non-Amish	CI (95%)	<i>p</i> - value
Age (years)	72.09 ± 8.82	74.40 ± 6.37	-5.58 to 0.96	0.16 [#]
DV3 (mm ³)	0.03 ± 0.03	0.03 ± 0.02	-0.01 to 0.01	1 [#]
DV5 (mm ³)	0.04 ± 0.04	0.03 ± 0.02	-0.01 to 0.02	0.15 [#]
NCI	0.33 ± 0.09	0.32 ± 0.09	-0.03 to 0.05	0.59 [#]
CT (μm)	151.45 ± 37.37	154.07 ± 33.37	-17.47 to 12.24	0.73 [#]

DV3: drusen volume in 3 mm circle; DV5: drusen volume in 5 mm circle; CT: choroidal thickness; NCI: normalized choroidal intensity. Results are expressed as mean ± SD.

[#] Insignificant levels between Amish and non-Amish groups.

Table 3

Pearson correlations between DV, age and CT in Amish and non-Amish population.

Groups		Amish		Non-Amish	
		DV3	DV5	DV3	DV5
Age (years)	Pearson (r)	-0.07	0.08	-0.14	-0.12
	<i>p</i> - value	0.61 [#]	0.54 [#]	0.39 [#]	0.44 [#]
CT (μm)	Pearson (r)	- 0.08	- 0.16	0.60	0.04
	<i>p</i> - value	0.56 [#]	0.26 [#]	0.71 [#]	0.81 [#]

DV3: drusen volume in 3 mm circle; DV5: drusen volume in 5 mm circle; CT: choroidal thickness; NCI: normalized choroidal intensity.

[#] Insignificant correlations between DV, age and CT.

Table 4

Linear regression analysis between DV, age and choroidal parameters (NCI and CT) in Amish and non-Amish groups.

	Model	r	r ²	Adjusted r ²	Std. error of the estimate	p - value
Amish	1	0.32	0.10	0.08	0.03	0.02 [*]
	2	0.42	0.18	0.16	0.04	0.002 [*]
Non- Amish	1	0.33	0.11	0.08	0.02	0.04 [*]
	2	0.33	0.11	0.09	0.02	0.03 [*]

Model 1: Drusen volume in 3 mm circle against age, CT and NCI

Model 2: Drusen volume in 5 mm circle against age, CT and NCI

^{*} Significant predictors: (constant), NCI