OPTICAL COHERENCE TOMOGRAPHY–BASED CORRELATION BETWEEN CHOROIDAL THICKNESS AND DRUSEN LOAD IN DRY AGE-RELATED MACULAR DEGENERATION

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Abstract

Purpose—Spectral domain optical coherence tomography can be used to measure both choroidal thickness and drusen load. The authors conducted an exploratory study using spectral domain optical coherence tomography to determine if a correlation between choroidal thickness and drusen load exists in patients with dry age-related macular degeneration.

Methods—Forty-four patients with dry age-related macular degeneration were recruited. The drusen area and volume were determined using the automated software algorithm of the spectral domain optical coherence tomography device, and choroidal thickness was measured using enhanced depth imaging. Correlations were determined using multivariable and univariable analyses.

Results—The authors found an inverse correlation between choroidal thickness and drusen load ($r = -0.35$, $P = 0.04$). Drusen load was also correlated with visual acuity ($r = 0.32$, $P = 0.04$). A correlation between choroidal thickness and visual acuity was suggested ($r = -0.22$, $P = 0.21$).

Conclusion—Spectral domain optical coherence tomography can be used to assess the correlation between drusen load and choroidal thickness, both of which show a relationship with visual acuity. The measurement of these outcomes may serve as important outcome parameters in routine clinical care and in clinical trials for patients with dry age-related macular degeneration.

Keywords

adult choroid/anatomy and histology; choroid/blood supply; disease progression; humans; macular degeneration/pathology; retinal photoreceptors/pathology; retinal drusen/etiology; retinal drusen/pathology; tomography; optical coherence

Age-related macular degeneration (AMD) is one of the leading causes of vision loss in people over the age of 50 in the developed world. The role of the choroid in the pathogenesis and progression of dry AMD through the formation and accumulation of drusen deserves further investigation. The choroid provides the only circulation for the retinal pigment epithelium (RPE) and outer retina. Therefore, it is the primary means of metabolic support for these tissues.¹ It has been shown that the choriocapillaris has unique features including high flow rate and low oxygen extraction that are mandatory to sustain normal photoreceptor metabolism.³ Hence, the choroid's critical role of metabolic support for the retina and RPE suggests that this vascular layer may have a role in drusen development. In other words, RPE with poor metabolic support secondary to deficient choroidal supply may be more prone to developing drusen as they are unable to completely metabolize photoreceptor byproducts.^{4,5}

Spectral domain optical coherence tomography (SD-OCT) is a relatively new technology that allows detailed imaging within the retina, including the photoreceptor layer and RPE, as well as the choroid.⁶ High-definition SD-OCT has previously been used to measure choroidal thickness in AMD.⁷ It has been demonstrated that enhanced depth imaging (EDI) SD-OCT, which produces an inverted image from 100 scans to improve signal-to-noise ratio, can be used to visualize the choroid even better.^{8–11} The new technology has led to better understanding of the role of choroid in various macular diseases, including central serous chorioretinopathy,^{9–11} high myopia,^{12,13} Vogt–Koyanagi–Harada disease,¹⁴ and a variety of retinal dystrophies.¹⁵ However, although SD-OCT has been used to assess choroidal thickness in various diseases, including AMD, it has not yet been used to correlate choroidal thickness with drusen load in dry AMD.

In addition to measuring choroidal thickness, SD-OCT can now be used to measure drusen load (area and volume). This novel diagnostic technology and algorithm was evaluated and showed the ability to generate highly reproducible qualitative and quantitative analysis of the drusen area and volume.¹⁶ It also demonstrated the capacity to illustrate undulating changes in drusen area and volume over time.¹⁷ With the advent and availability of SD-OCT, EDI, and reliable measurements of drusen area and volume, the relationship between choroidal thickness and dry AMD can now be more accurately studied. To the best of our knowledge, this is the first study examining the relationship between choroidal thickness and drusen load in dry AMD using SD-OCT.

Methods

This study was approved by the Research Ethics Board at the University of British Columbia. Patients with a clinical diagnosis of dry AMD currently under care of the retina service at the University of British Columbia (D.A.A., F.F., A.W.K., A.B.M.) were asked to participate. Inclusion criteria included the following: aged 55 years or older at the time of

recruitment, dry AMD diagnosed in both eyes, and no evidence of other macular disease (diabetic retinopathy, epiretinal membrane, vitreomacular traction, etc). Exclusion criteria were the following: past or present diagnosis of wet AMD, geographic atrophy, and significant ocular media opacity.

Patients underwent a full ophthalmic examination, including measurement of best-corrected visual acuity, intraocular pressure, biomicroscopy, and dilated fundus examination. Snellen visual acuity was converted to logarithm of minimal angle of resolution (logMAR) equivalents for statistical analysis. Cirrus SD-OCT (version 6 software; Carl Zeiss Meditec, Inc, Dublin, CA) was used. Each eye was scanned once using a cube scan protocol (200 × 200 cube scan). In the same single session, each eye was also scanned a minimum of two times with the EDI raster scan. Each scan was centered on the fovea automatically and covered a 6 × 6-mm area. The minimum required signal strength for every scan was 6 of 10.

The drusen volume and area data used in this study for analysis were automatically generated by the Cirrus SD-OCT software algorithm from the cube scans. For measurement of choroid thickness, three independent investigators measured the choroidal thickness beneath the fovea manually from the EDI raster images using the program's caliper function during two different sessions. The scan with the best signal strength score was chosen for each eye. Each researcher was blinded to the measurements of others and to their own measurements from previous sessions.

Sample characteristics were described as frequency (percent) for categorical variables and as mean (standard deviation [SD]) for continuous variables. Intra- and interrater reliability of the measurement of choroid thickness was assessed using intraclass correlation coefficients and limits of agreement determined by fitting a linear mixed model. The association between the drusen area and choroid thickness was assessed using a general linear regression model. The drusen area values were square root transformed to better meet the assumptions of normality and homogeneity of variance, and generalized estimating equations were used to account for the within-person correlation arising from both eyes. We repeated the analysis adjusting for age and sex. Similar analyses were used to assess the association between choroid thickness and visual acuity. Stata v12.1 (StataCorp. 2011. Stata Statistical Software: Release 12; StataCorp LP, College Station, TX) was used for all analyses.

The sample size was one of convenience; it represented the number of patients who could be recruited with the resources available for the study. No formal a priori sample size calculation was made.

Results

Participant enrollment took place between February 2012 and May 2012. A total of 44 subjects were recruited with the initial diagnosis of bilateral dry AMD, of which 31 were women (70%). The average age of all subjects was 75.7 years (SD, 8.4 years; range, 60–91 years).

The mean signal strength for the cube scans was 7.91 (SD, 0.98), and all signal strengths were 6 or greater. The mean signal strength for the EDI raster scans was 8.45 (SD, 1.11). All

but one patient had signal strength greater than 6. The one subject had signal strength of 5 in both eyes, which could not be improved on multiple attempts. Forty patients were taking Age-Related Eye Disease Study vitamin supplementation (91%). None of the patients were current smokers; 8 patients (18%) were previous smokers who had quit between 13 and 49 years ago. The mean visual acuity was 0.39 logMAR (SD, 0.29) for right eyes and 0.36 logMAR (SD, 0.23) for left eyes.

Average (across eyes) intrarater intraclass correlation coefficients for the 3 raters were 0.87, 0.80, and 0.64. The average interrater intraclass correlation coefficient was 0.67. Although these intraclass correlation coefficient values are considered acceptable,¹⁸ the limits of agreement between any 2 raters were in the range of -100 to 100 μ m (~40% of the average choroid thickness) indicating substantial absolute disagreement between the raters. We considered the average choroid thickness across all three raters to be the best estimate of choroid thickness, and this was used in our statistical analyses.

We found a strong correlation between the drusen area and drusen volume (Figure 1, $r = 0.86$). Given this finding and that the square root of the drusen area better fit the model assumptions rather than the cubic root of the drusen volume, only the square root of the drusen area was used for further data analysis. Neither age nor gender was statistically significant in any of the models nor did their inclusion result in changes to the effect estimate. Not surprisingly, given the small sample size, the inclusion of these variables spuriously increased the standard error of the estimates (Table 1) and so we focus our interpretation on the results of the univariable analyses.

An inverse relationship between the drusen area and choroidal thickness (Figure 2, $r = -0.35$; $P = 0.04$) was shown, demonstrating that patients with thinner choroid tended to have greater drusen load. The relationship between the drusen area and choroid thickness was independent of age and gender.

We looked at the relationship between the drusen area and visual acuity of the subjects. Figure 3 illustrates a positive correlation between the drusen area and visual acuity ($r = 0.32$, $P = 0.04$). Patients with greater drusen load tended to have worse visual acuity, and this was independent of choroidal thickness. Finally, an inverse relationship between choroid thickness and visual acuity was seen (Figure 4, $r = -0.22$, $P = 0.21$), independent of drusen area, showing that thinner choroid is associated with poorer visual acuity. However, this result was not statistically significant and should be interpreted cautiously.

Discussion

This exploratory study using SD-OCT shows that a correlation exists between choroidal thickness and drusen load in patients with dry AMD. Spectral domain OCT has previously been used to measure choroidal thickness in dry AMD,⁷ but its ability to demonstrate a correlation between choroidal thickness and drusen load in dry AMD has not yet been illustrated. We also found a strong correlation between the drusen area and drusen volume. This suggests that either the drusen area or the drusen volume alone may be enough as a parameter for monitoring dry AMD.

Our study found an inverse relationship between drusen load and choroidal thickness using SD-OCT. Choroid is normally thickest under the fovea, and it decreases with age.^{13,19–23} Foveal choroidal flow and volume also decrease with age.²⁴ Grunwald et al.²⁴ hypothesized that this was in response to age-related decrease in density and diameter of the choriocapillaris that was previously observed by Ramrattan et al.²⁵ A more recent study found an inverse relationship between choroidal blood flow (and volume) and drusen extent.¹ Another study also found that the eyes with the most drusen had the lowest choriocapillaris density.²⁶ It is not yet clear as to the reason for the inverse relationship. Berenberg et al.¹ hypothesized that choroidal thinning may be because of drusen creating a distribution barrier to the trophic substances necessary for proper choriocapillaris maintenance. Inversely, they also hypothesized that thinner choroid and decreased blood flow result in decreased waste removal from the structures it supports, ultimately leading to drusen formation.

In addition, our study found that the drusen area correlated inversely with the visual acuity. This may be because of the fact that drusen represents disruption of RPE, the Bruch membrane, and choriocapillaris, subsequently affecting the health of the overlying photoreceptors.²⁷ A study using SD-OCT showed that the photoreceptor layer over drusen was decreased in thickness compared with that of controls.²⁸ A more detailed observation using SD-OCT revealed that drusen causes disruption to the structural integrity within the photoreceptor layer, namely at the inner and outer segment junction, although it was also shown that the disruption may be restored after drusen regression.²⁹ Unhealthy photoreceptors, or their atrophy, would lead to subjects' functional deficits in the form of decreased visual acuity.³⁰ A correlation between choroidal thickness and visual acuity was also suggested in our study, but this did not reach a conventional level of statistical significance. This result could be expected with reasonable confidence because another group has also recently shown an inverse correlation between choroidal thickness and visual acuity in myopia.¹³ It is important to note that their study showed that subfoveal choroidal thickness was the only significant predictor for visual acuity while other parameters, including retinal and foveal thickness, outer retinal hyporeflective layer thickness, and inner segment to RPE aggregate thickness, were not significant predictors. They ultimately concluded that OCT-measured retinal features are not correlated with visual acuity. Our study supports their finding that choroidal thickness is a reliable indicator of visual acuity. Choriocapillaris plays an important part in the health of photoreceptors along with RPE and the Bruch membrane.²⁷ Similar to the effects of drusen, the decrease in choroidal thickness, and therefore blood flow, could compromise the health of the photoreceptors and subsequently lead to their functional decrease and decreased visual acuity.

Optical coherence tomography parameters have been used as outcome measures in various clinical trials for wet AMD.^{31,32} Not only were OCT criteria an outcome measure in these trials but they were also used as part of treatment criteria. However, to date, there has been a paucity of clinical trials for dry AMD. One reason for this is that the anatomical progression of dry AMD is very slow and at times even undetectable. The same may be said for vision loss secondary to dry AMD. Thus, these changes often take months to years to be realized,⁶ and as a result, no imaging modality has yet been shown to be superior to other modalities as for measuring outcome parameters in dry AMD studies.⁶ Spectral domain OCT outcomes are now being incorporated into dry AMD studies. To date, SD-OCT has mostly been used

to measure geographic atrophy in AMD trials.^{33,34} As SD-OCT has been demonstrated to be a promising tool in assessing drusen morphology,^{16,17,35} it is now being used to evaluate drusen in some dry AMD trials as well.⁶ Currently, a clinical trial is underway using SD-OCT to study the effects of eculizumab on the growth of both geographic atrophy and drusen volume in dry AMD patients.^{6,36} The Age-Related Eye Disease Study 2^{6,37} is currently attempting to determine if SD-OCT can be used to predict disease progression and vision loss by using it to observe various parameters, including drusen volume and geographic atrophy.⁶ Our study suggests that other SD-OCT parameters like choroidal thickness may also be useful outcome parameters in dry AMD trials. However, the moderate interrater agreement that we observed in the measurement of choroid thickness suggests that other methods for measuring choroid thickness, such as automated algorithms,³⁸ may be more reproducible than manual measurements. Furthermore, diurnal fluctuations in choroidal thickness^{39,40} would need to be accounted for in the clinical use of these measurements.

To our knowledge, this is the first study using SD-OCT to show that a correlation exists between choroidal thickness and drusen load in patients with dry AMD. Furthermore, an inverse relationship was shown between visual acuity and both choroid thickness and drusen load. Our data suggest that SD-OCT parameters such as choroidal thickness and drusen load may not only be useful in the management of patients with dry AMD but may also be used as outcome parameters in clinical trials of dry AMD.

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Fig. 1.
Linear regression analysis of drusen volume versus drusen area.

Fig. 2.
Univariable linear regression analysis of drusen area versus choroid thickness.

Fig. 3.
Univariable linear regression analysis of drusen area versus visual acuity.

Fig. 4.
Univariable linear regression analysis of choroid thickness versus visual acuity.

Table 1

Results of Univariable and Multivariable Regression Analyses

Outcome	Predictor	Beta (SE)	P	Model R ² (P)
Drusen area	Choroid thickness	−0.0025 (0.0012)	0.04	0.12 (0.04)
Drusen area	Choroid thickness	−0.0022 (0.0012)	0.07	0.13 (0.04)
	Age	0.006 (0.009)	0.50	
	Female	−0.19 (0.16)	0.23	
Drusen area	Visual acuity	0.65 (0.31)	0.04	0.10 (0.04)
Drusen area	Visual acuity	0.61 (0.33)	0.07	0.19 (0.001)
	Age	−0.001 (0.009)	0.89	
	Female	−0.17 (0.14)	0.22	
	Choroid	−0.002 (0.001)	0.08	
Choroid thickness	Visual acuity	−19.5 (15.7)	0.21	0.05 (0.21)
Choroid thickness	Visual acuity	−8.2 (14.4)	0.57	0.12 (0.19)
	Age	−1.2 (0.9)	0.18	
	Female	13.7 (18.6)	0.74	
	Drusen area	−8.4 (10.4)	0.42	

Beta, regression coefficient; SE, standard error; drusen area, square root of drusen area.