Relationship between Outer Retinal Thickness Substructures and Visual Acuity in Eyes with Dry Age-Related Macular Degeneration


PURPOSE. To explore the correlation between outer retinal substructures and visual acuity in dry age-related macular degeneration (AMD).

METHODS. Analysis of spectral domain optical coherence tomography datasets from 100 eyes of 100 consecutive patients with dry AMD was performed. The internal limiting membrane, outer nuclear layer (ONL), external limiting membrane (ELM), inner segment-outter segment (IS-OS) junction, outer photoreceptor border, inner and outer retinal pigment epithelium (RPE) borders, and Bruch’s membrane, were manually segmented by Doheny Image Reading Center (DIRC) graders. Areas, thicknesses, and volumes of RPE, IS, OS, ONL, and the total retina in the foveal central subfield were correlated with the logarithm of minimal angle of resolution (logMAR) visual acuity using univariable and multivariable regression analysis.

RESULTS. The visual acuity in this group ranged from logMAR 0 to 1.3 with a mean of 0.23. Areas, thicknesses, and volumes of ONL, IS and OS, thicknesses of total retinal and RPE, and intensities of IS, OS, and RPE, showed statistically significant association (P < 0.05) with logMAR best corrected visual acuity. The highest correlations were observed for the ONL (thickness: r = −0.49, volume: −0.47, area: −0.50) and photoreceptor IS (thickness: −0.59, area: −0.63, volume: −0.53). The model with the highest correlation in this study included thicknesses of ONL, IS, OS and RPE, as well as area of ONL, IS, OS, and RPE, and intensity of RPE.

CONCLUSIONS. Although integrity of outer retinal substructures in the foveal central subfield correlates with visual acuity in the eyes of patients with dry AMD, the correlation is only moderate and does not fully explain the variability in acuity in these cases. (Invest Ophthalmol Vis Sci. 2011;52:6743–6748) DOI: 10.1167/iovs.10-6723

Color photography has traditionally been the gold standard modality for classifying, staging, and quantifying neovascular or dry age-related macular degeneration (AMD), and for monitoring its progression over time.1 More recently, fundus autofluorescence (FAF) imaging has been touted for its superior contrast in identifying and quantifying the features of dry AMD, including geographic atrophy. Areas of hyper autofluorescence with blue light FAF have been shown to be associated with early structural damage and functional loss in cases of dry AMD.2 Different patterns of abnormal FAF have also been described and are believed to represent early changes in dry AMD.2 More recently, near infrared autofluorescence (NIA), a technique for assessing melanin content (also present in retinal pigment epithelium [RPE]), has also been used to demonstrate abnormalities in dry AMD which have been suggested to represent areas of RPE damage.3 FAF imaging, however, does not appear to be the optimum tool for quantitative assessment of earlier features of dry AMD such as drusen, and subtle photoreceptor and RPE alterations. As a result, several investigators have explored the feasibility of using optical coherence tomography (OCT) to study dry AMD, particularly with the development of spectral domain OCT (SDOCT) devices, which feature higher resolution, higher speed, and higher sensitivity compared with time-domain OCT.

Schuman and colleagues used SDOCT to identify and classify several different phenotypes of drusen, and also noted thinning of the photoreceptor layer overlying these drusen.4 Freeman and coworkers performed manual segmentation to quantify drusen volumes and correlated them with Age Related Eye Disease Study (AREDS)-based drusen areas, but did not quantify other outer retinal structures.5 Fleckenstein and colleagues used SDOCT imaging to study the structural alterations that occur in the retina at the junctional zone between atrophic and uninvolved retina in patients with advanced dry AMD, and noted progressive alterations in the various outer hyperreflective bands.6 Dinc and coworkers performed microperimetry in patients with intermediate AMD and found evidence of subclinical macular function loss.7 Midena et al. also found similar microperimetric abnormalities and correlated them with FAF abnormalities, but did not correlate them with OCT.
findings.\(^8\) Thickening at the foveal site in geographic atrophy not involving fovea described by Schnitz-Valckenberg et al. may reflect a preapoptotic stage of neuronal cellular elements indicating imminent atrophy.\(^9\) Several investigators, including our group, have studied the relationship between OCT features, outer retinal substructures, and visual function.\(^10\)–\(^12\) Landa et al. studied the relationship between inner segment-outer segment (IS-OS) junction and visual acuity but did not take into account the quantitative assessment of other outer retinal structures.\(^13\) The relationship between these structures and visual acuity in patients with dry AMD, however, has not been studied quantitatively.

In this study, we report the relationship between visual acuity and outer retinal structural alterations, as quantified by manual segmentation of SD-OCT scans, in a cohort of subjects with varying stages of dry AMD.

Materials and Methods

Data Collection

OCT data were collected from 100 consecutive patients with dry AMD who presented to a tertiary retina practice at the Doheny Eye Institute between September 2006 and March 2009. Approval for data collection and analysis was obtained from the institutional review board of the University of Southern California and the research adhered to the tenets set forth in the Declaration of Helsinki. To be included in the study, patients were required to have undergone macular cube (512 x 128) examination using a single spectral domain OCT (Topcon 3D OCT 1000, Topcon Medical Systems, Paramus, NJ), and were required to have clinical features of dry AMD, ranging from intermediate drusen alone to advanced stages of geographic atrophy. Patients with any evidence of other ocular disease associated with retinal structural changes, or reduced vision, were excluded. Cases that did not have sufficient image quality to permit retinal layer boundary grading were also excluded. Best corrected visual acuity was obtained using Snellen visual acuity charts for all patients. Raw image data were exported from the OCT system for analysis at the Doheny Image Reading Center.

Grading Software and Protocol

For all OCT analyses, previously described and validated software developed by Doheny Eye Institute (3D OCTOR) was used to display the 128 B-scans for each case and perform quantitative assessments.\(^14\) The 3D OCTOR software effectively operates as a paint program and a calculator allowing the grader to manually draw multiple boundaries to define structures of interest. Once the segmentation lines are drawn, the software calculated the distance in pixels between the boundary lines for each of the various defined spaces. By using the dimensions of the B-scan image, the calculated pixels are converted into micrometers to yield a thickness measurement at each location. The thickness at all unsampled locations between the line scans are then interpolated using a linear approximation to yield a thickness map. Previously, we have demonstrated that this approach yields measurements identical to those provided by the OCT instrument itself when boundaries are placed in the same locations.\(^14\) After interpolation, thickness values may be simply converted into volumes (cubic millimeter) by multiplying the average thickness measurement by the sampled area. Mean thickness values and volumes can be generated for any zone including the 9 Early Treatment of Diabetic Retinopathy Study macular subfields that are commonly used in clinical practice. For the purpose of this study, because OCT findings were being correlated to distance visual acuity, we focused only on the foveal central subfield (FCS), and manual segmentation efforts were restricted to those portions of the various B-scans which contributed to the FCS calculation. Furthermore, our previous study found that thickness values within the Early Treatment of Diabetic Retinopathy Study subfields were unchanged if only every fourth scan from the 128 B-scan volume cube was used for the purpose of the calculation.\(^14\) Thus manual segmentation boundaries were only drawn on every fourth scan.

On these selected B-scans passing through the FCS, the following boundaries were manually drawn by certified Doheny Image Reading Center OCT graders (RRP and YO): internal limiting membrane (ILM), inner border of outer nuclear layer (ONL), external limiting membrane (ELM), photoreceptor inner segment and outer segment junction (IS-OS junction), outer border of the photoreceptor layer (PRL), inner border of the RPE, outer border of RPE, and Bruch’s membrane (Fig. 1). The ILM was identified at the interface between the vitreous and the neurosensory retina (eyes with epiretinal membranes or vitreoretinal interface disease were not included in this cohort and thus did not confound this assessment). Because of angle-of-incidence-related variability in the appearance of Henle’s fiber layer, the inner border of the outer nuclear layer was selected at the outer aspect of the thin bright band corresponding to the inner one-third of the outer plexiform layer (i.e., the dark/nonvisible portions of the outer plexiform layer were included in the segmented ONL). The RPE band (inner aspect) was identified as the brightest band just anterior to the dark thin choriocapillaris band. The RPE band was also useful as a reference to help identify the thin highly-reflective IS-OS band just internal to the RPE.
Statistical Analyses

Snellen visual acuity was converted to logarithm of minimal angle of resolution visual acuity (logMAR) for the purposes of statistical analysis. Univariate and multivariate regression was used to test for associations between visual function parameters and OCT parameters. Stepwise regression was used for selection of independent parameters. Disagreement regarding manual segmentation of retinal layers was resolved by open adjudication. All OCT scans included in the study met reading center criteria for sufficient image quality, including the absence of significant artefactitious variations in signal intensity or generalized reductions in signal strength. No minimum value for signal strength was set, as manual grading with the software (3D OCTOR; Topcon Medical Systems) often allows quantitative information to be accurately derived from images with low signal strength: if any boundary was discontinuous or not visible, it was left undrawn in this portion of the B-scan. The mean thickness, area, volume and intensity of total retina (outer photoreceptor layer to ILM), ONL, photoreceptor inner segments, photoreceptor outer segments, and RPE were then computed. When calculating the volume and area, the areas where the layer was not drawn were excluded. To assess reliability of the manual segmentation approaches, a randomly chosen subset of cases (50) was regraded by a third, independent, masked grader (MGN) 12 months after the initial grading.

RESULTS

Baseline Characteristics

The mean age of the 100 subjects was 80.18 (range 57–96), and 55% were females. The visual acuity in this group ranged from logMAR 0 (approximately 20/20) to 1.3 (approximately 20/100) with a mean of 0.25 (approximately 20/52). Fifty-five patients were phakic and the remaining 45 were pseudophakic. Total retina, ONL, photoreceptor inner segments, photoreceptor outer segments, RPE thickness, area, volume, and intensity values from the manual segmentation analyses are shown in Table 1.

Multivariable Regression

Using visual acuity as the dependent variable, stepwise multivariate regression was performed which yielded multiple different models with $R^2$ value ranging from 0.45 to 0.61. The

| OCT Parameter | Mean $\mu m$ $\mu m^2$ $\mu m^3$ Intensity | Correlation Coefficient $r$ $r^2$ $P$ |
|---------------|------------------------------------------|-----------------------------------|------------|----------|----------|----------|
| Total Retina  | 249.63 0.78 0.2 0.29                   | -0.35 0.14 -0.35 -0.03           | 0.125 0.14 0.124 0.001         | <0.001 0.174 <0.001 <0.001 |
| Outer Nuclear Layer | 104.33 0.14 0.08 0.25 | -0.49 -0.50 -0.47 -0.1 | 0.236 0.253 0.225 0.01 | <0.001 <0.001 <0.001 0.327 |
| Inner Segment | 16.28 0.55 0.01 0.29 | -0.59 -0.63 -0.53 -0.27 | 0.349 0.393 0.281 0.07 | <0.001 <0.001 <0.001 0.007 |
| Outer Segment | 16.46 0.51 0.01 0.33 | -0.44 -0.41 -0.43 -0.29 | 0.189 0.172 0.186 0.081 | <0.001 <0.001 <0.001 0.004 |
| RPE           | 32.09 0.76 0.03 0.50 | -0.18 -0.43 -0.13 -0.52 | 0.043 0.182 0.017 0.273 | <0.001 0.071 0.191 <0.001 |

The parameters which showed stronger association with visual acuity are shown in bold.
Although RPE intensity appeared to be important, RPE thickness or area did not correlate well with the visual acuity. There may be several reasons for this. Though the precise pathogenesis of AMD is unknown, it is generally believed that the photoreceptors, RPE, Bruch’s membrane, and choroid are involved. Which structure is damaged primarily or is the inciting or triggering factor is also not well established, though many believe initial damage to the RPE leads to secondary changes in the retina and choroid.19-20 The RPE may be functionally compromised with consequent damage to the overlying photoreceptors, however, before thinning and frank loss of the RPE occur. This observation would appear to be consistent with the finding by Schuman and coworkers that the photoreceptor layer appears thinner overlying drusen1 and the observations of Bearelly and colleagues who noted evidence of alterations to the photoreceptors before the RPE at the edges of geographic atrophy (GA).15 Another potential explanation for the lack of correlation with visual function may be the changes occurring in Bruch’s membrane in dry AMD. Bruch’s membrane is known to increase in thickness15,16 in dry AMD due to the accumulation of basal laminar and basal linear deposits. Basal laminar deposits in particular are difficult to distinguish from the outer RPE border and may have compensated for any reduction in RPE cell thickness.

In the multivariate analyses, the best final model for prediction of visual acuity included the thicknesses of the outer retinal structures and the intensities of all the layers of retina. This would again highlight the importance of reflectivity parameters and media clarity in predicting visual acuity. The cumulative $R^2$ of the most predictive model was 0.61, suggesting that 39% of the variability in visual acuity remains unexplained. There are several potential explanations which include the fact that while we considered the foveal central subfield, we did not consider smaller zones such as the foveola itself. For example, a subject could have an eccentrically positioned zone of atrophy which involved the foveal central subfield but not the foveal center itself. Such a patient may have significant reduction in thickness values for the various layers, but good visual acuity. Extrarfoveal fixation that is known to develop in patients with geographic atrophy involving fovea could be another reason.53 In addition, structural changes do not always temporally coincide with functional changes. For example, a cell may become dysfunctional but may still appear normal on imaging studies.

While the strengths of this study include the careful segmentation of OCT data in a certified OCT reading center using grading protocols shown to be reproducible, there are several limitations to be considered. First, this is a retrospective analysis, and there may be confounding factors which remain unaccounted for. Second, while dense spectral domain OCT data were collected, thickness calculations still required interpolation between the graded B-scans. Third, the B-scans in this study were acquired without averaging or oversampling, which has been shown to increase the visibility of outer retinal structures, especially the ELM. Thus, structures which were not drawn because they were felt to be missing or discontinuous may

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICC</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Total retinal thickness</td>
<td>0.823</td>
<td>0.421-0.946</td>
</tr>
<tr>
<td>Outer nuclear layer thickness</td>
<td>0.803</td>
<td>0.353-0.940</td>
</tr>
<tr>
<td>Inner segment thickness</td>
<td>0.863</td>
<td>0.552-0.958</td>
</tr>
<tr>
<td>Outer segment thickness</td>
<td>0.924</td>
<td>0.752-0.977</td>
</tr>
<tr>
<td>RPE thickness</td>
<td>0.713</td>
<td>0.061-0.913</td>
</tr>
</tbody>
</table>

CI, confidence interval.
have in fact been present but not clearly visible due to the quality of the scan. Moreover, the model developed from this study may not generalize and may only be applicable to the tertiary care retina practice population that was included in this analysis. Finally, we considered a limited number of sub-structures and parameters in this study; it is possible that additional parameters could yield more predictive models.

In summary, quantitative OCT measurements of the outer retinal structures, including both morphometric and reflectivity parameters, correlate moderately with visual acuity in dry AMD. The correlation does not fully explain the variability in visual acuity, but is more predictive than conventional neurosensory retinal thickness. These findings and the model developed in this study may be useful for generating indices of the integrity of the fovea which may be tested in future investigations.

References


