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Effect of change in drusen evolution on photoreceptor inner segment/outer segment junction

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Abstract

Purpose—To evaluate the integrity of photoreceptor inner segment/outer segment (IS/OS) junction after change of drusen size in age-related macular degeneration (AMD) using spectral domain optical coherence tomography (SD-OCT).

Methods—Drusen volume raster scans were performed with the Spectralis SD-OCT (Heidelberg Engineering) through 2624 drusen in 14 eyes with clinically dry AMD who had been longitudinally followed between 23–28 months without intervention (mean 26.3 months). All eyes had ETDRS visual acuity. A total of 416 out of 2624 drusen were analyzed.

Results—Of 416 drusen, 83 (20%) were found to have regressed spontaneously (group A), 212 (51%) showed no change in size (group B) and 121 (29%) progressed (group C). Mean drusen size of all drusen was 63.7 ± 25.7 microns. Cross-sectional analysis of drusen morphology showed a correlation between drusen size and disrupted IS/OS junction/photoreceptor integrity ($r = -0.48$, $p < 0.001$). Of the drusen that regressed over time there was intact IS/OS junction integrity. Even drusen that caused a major disruption showed IS/OS restoration in 74% of the drusen ($p < 0.001$).

Conclusions—Progression of drusen shows structural disruption of the IS/OS-junction. After drusen regression the IS/OS-junction is either able to restore as drusen regress or was artifactuously compressed and not initially visible due to the initial drusen compression of the IS/OS junctional line. Therefore drusen evolution may play an important role in affecting the photoreceptor IS/OS-junction integrity.

Introduction

Drusen are the hallmark findings in age related macular degeneration (AMD). They have been intensively studied clinically as well as histologically in order to better understand the pathology of the disease.^{1–3}

Drusen are extracellular deposits between the RPE and Bruch's membrane. The analysis of drusen microstructure and genetic risk factors have revealed a low-grade inflammation in drusen biogenesis and an abnormal regulation of the complement system.⁴ Drusen have been shown to induce degeneration of retinal pigment epithelium (RPE) cells and enlarge in size and number with the progression of AMD. These changes cause hypoxia and mechanical stress to the overlying photoreceptors.^{1,5}

Drusen become clinically associated with a higher risk of vision loss when they exceed 64 microns in width.⁶ This observation was based on the use of color fundus photography, the

only available imaging technique to monitor early AMD prior to the appearance of optical coherence tomography (OCT). Changes in early AMD, such as progression or disappearance of drusen, were evaluated based on color photographs using the Age Related Eye Disease Study (AREDS) system.⁷ Color photographs are limited, however, and are not able to provide measurements such as drusen volume or detect changes in outer retinal layers.

The use of optical coherence tomography (OCT) with high-speed and high-resolution images has increased during the last years and has become an important tool to monitor macular diseases.^{8,9} The spectral domain-OCT (SD-OCT) has a 3 to 7 μm axial depth resolution and an 11- μm lateral resolution allowing for a very detailed information at the outer retinal layers such as drusen thickness and RPE defects in well defined areas.¹⁰ A previous study by our group showed that it is possible to determine drusen volume in an eye based on volume raster scans using a SD-OCT device.¹¹

The “Five-Year Incidence and Disappearance of Drusen and Retinal Pigment Epithelial Abnormalities” was a study that demonstrated that large drusen were replaced by numerous small drusen.⁷ The study also discussed the fact that the underlying disease might still be present in eyes in which drusen have disappeared from the entire macula. Studies reporting drusen disappearance have been mainly based on color fundus photographs, which do not permit evaluation of drusen height or evaluation of outer retinal changes. These studies do not comment on changes in drusen size and therefore do not draw conclusions on how drusen size may affect outer retinal layers. For this reason, we have used the SD-OCT to image drusen longitudinally to determine the effect of drusen evolution on photoreceptor inner segment/outer segment junction integrity.

Methods

Patients

This observational study was performed at the Jacobs Retina Center La Jolla of the University of California, San Diego. Patients with clinical dry AMD and drusen were enrolled for imaging and were available for follow up visits for a mean time of 26.3 months (median 26.5 months, range 23 to 28 months). All patients had ETDRS visual acuity better than 20/25. This study adhered to the tenets of the Declaration of Helsinki. The UCSD IRB approved it and all subjects were consented prior to enrollment. Only eyes without prior treatment (other than vitamins as our patient varied in vitamin regimens and compliance) at time of enrollment and during follow up visits were included in the study. Most patients took preventive nutritional supplements such as the Age-Related Eye Disease Study (AREDS) formula, lutein, zeaxanthin and omega-3 fatty acid. Eyes with hard and soft drusen were included in the study. Eyes with pigment epithelial detachment, geographic atrophy, neovascular AMD or eyes having had prior laser treatment for drusen were excluded. Other retinal diseases such as diabetic retinopathy or cystoid macular edema were also excluded.

Spectral domain optical coherence tomography (SD-OCT)

Patients were imaged with the Heidelberg Retina Angiograph 2 with a combined SLO/SD-OCT instrument (Spectralis HRA2+OCT; Heidelberg Engineering, Heidelberg, Germany) by one experienced examiner (KH). The device contains a real-time eye movement tracking system that allows to capture multiple scans at an identical retinal location and identifies exactly the same location throughout follow-up scans at different time points. Fundus autofluorescence (FA) images and raster volume scans were also performed. The macular region was scanned using a protocol that was developed to determine drusen volume with a field of view $30^\circ \times 30^\circ$ and an image resolution of 1536×1536 pixels.¹¹ Raster volume

scans consisted of 96 scans images spaced 60 μm apart, and covered a 6 mm by 6 mm area of each eye centered at the fovea. An infrared (IR) fundus image of the retina was taken simultaneously by the SLO and used to determine the orientation of the OCT scans. The accuracy of the SLO and OCT image overlap was calibrated with the alignment tool provided by Heidelberg Engineering. This tool consists of a calibration target screen and calibration software. We used this alignment tool in regular intervals to ensure accurate image alignment between the SLO and OCT image. To ensure accurate alignment between the baseline and follow-up exam for each patient we used vessel outlines in the IR image and the image toggle mode to check for any image registration error and we used manual compensation to ensure proper alignment. Digital images were saved on a hard disc for further analysis and processing.

Measurement of Drusen Height

Drusen height was calculated based on the raster scans using the Heidelberg Spectralis SLO/OCT (Heidelberg Engineering, Vista, CA). Only scans that cut through the apex of the drusen were further analyzed. Lateral scans were evaluated to reassure the apex of the druse. Scans showing only the edge or a small detail of a druse were not used in our study. Drusen height was measured manually using the electronic caliper from the Spectralis software by one observer (figure 1). Intra-observer re-measurement of 10% of all drusen showed a small mean deviation of 11 μm ($\approx$ 1 pixel), intra-observer correlation is 0.9. The measurement included the base of the druse through the apex of the druse. After measurements, drusen were divided into 3 groups: regression (group A), stable (group B) and progression (group C). In order to delineate the regression and progression groups from the stable group, a decrease/increase of 30% of drusen height was used. This definition is based on the depth resolution of the OCT (7 μm equals one pixel), the accuracy of height measurement (11 μm obtained from masked re-measurement of drusen) as well as an average drusen height of 63 μm in our population. Taken together these measurements, the error was calculated 18 μm of 63 μm ($\approx$ 30%). The eye tracker of that device rejects any images where a lateral or rotational movement has been detected. Only images that overlap to the baseline image will be included in the scan. During the volume scan the acquisition will cease until proper alignment has been achieved and then acquisition will resume. We analyzed the potential effect of a lateral shift that might occur despite proper eye tracking. We modeled the druse as a circular structure and calculated the underestimation of drusen diameter based on this model. We found that for the average drusen size of 63 microns a lateral displacement of 30 microns entails only an error of 7 microns. Since a lateral displacement of 30 microns is easily detectable by our inspection procedure, we are confident that our results are reasonably accurate.

Grading of the inner-outer segment (IS/OS)-junction integrity score

We determined IS/OS junction integrity using a system we have previously published.¹² The horizontal scans through drusen apex were evaluated. The IS/OS disruption was graded from 0–3 (figure 2): Grade 3 meaning intact IS/OS layer, Grade 2 focal disruption of the IS/OS junction less than 50%, Grade 1 focal disruption of the IS/OS junction more than 50% and Grade 0 complete disruption of the IS/OS junction. Two independent experienced graders performed all grading of the IS/OS junction. A grading system with determination of the kappa reproducibility coefficient was used, as previously described.¹³ Two masked observers graded the IS/OS junction over drusen and in the areas of drusen disappearance. The correlation coefficient between the two graders for regression, progression, and structure integrity ranged from 0.81 to 0.9. This correlation coefficient is good for a structure as difficult to see. For that reason only one observer was used. No eyes were eliminated from the study due to inability to visualize the photoreceptor IS/OS layer.

Color fundus photographs

Color photos were used to validate drusen location and disease. Digital photographs of 30 and 50 degrees were taken with a Topcon fundus camera (Topcon, Tokyo, Japan) on the same day of imaging with SD-OCT. Although color pictures were taken, the AREDS classification was not used because it does not quantify drusen precisely in relation to overlying photoreceptors.

Statistics

Statistical analysis was performed using SPSS Version 18.0 (Chicago, IL). The Spearman correlation analysis was used to correlate drusen height and IS/OS-junction integrity score. For group comparison of photoreceptor integrity, a Kruskal-Wallis ANOVA was performed. A p value smaller than 0.005 was considered to be significant because of Bonferroni correction for multiple testing.

Results

A total of 2624 drusen out of 14 eyes with dry AMD were imaged with SD-OCT at the initial time point of patient enrolment using the drusen volume raster scan as described previously. 416 drusen (16%) of the total count showed scans through the apex of the drusen and were big enough for further evaluation. Of these 416 drusen 83 (20%) were found to have regressed spontaneously (group A), 212 (51%) showed no change in size (group B) and 121 (29%) progressed (group C). Progression, regression and no drusen change happened in 80% off all eyes, in the other 20% not all three phenomena appeared. These eyes only consisted of a small amount of drusen (mean 7 drusen). An example of each group is shown in figure 3. Mean drusen size of all drusen was 63.7 ± 25.7 microns (SD) (range 16 to 215).

In group A, 83 out of 416 drusen had spontaneously regressed by 31% to 100% in height (mean 88%). Initial drusen height ranged from 28 to 203 microns (mean $\pm$ SD: 78.8 ± 33.5 microns). 28 drusen (34%) partially regressed (mean regression was 64%) and 55 drusen (66%) completely disappeared. In group B, 212 drusen out of 416 drusen showed no change in drusen height during the period of follow-up. Mean drusen height was 63.8 ± 21.2 microns (range 20 to 215 microns) at initial measurement and 68.1 ± 24.2 (range 20 to 232 microns) at follow-up visit. In group C, 121 drusen out of 416 drusen progressed in size by 30% to 244% in height (mean 60%). Initial drusen height was 53.2 ± 21.5 microns (range 16 to 120 microns) and increased to 81.5 ± 29.4 microns (range 34 to 187 microns). Figure 4 summarizes all data.

Grading of the IS/OS junction showed higher grading scores (intact IS/OS) for smaller drusen and lower scores (defect IS/OS) for larger drusen (Figure 5). In group A, grading of the IS/OS junction integrity after drusen regression/disappearance demonstrated mostly intact photoreceptor integrity. In group B, grading of the IS/OS junction integrity did only vary little over time (mean difference -0.16). Group C showed a significant disruption of the IS/OS junction integrity after drusen growth. Figure 6 demonstrates drusen growth and disappearance in a single scan.

Cross-sectional analysis of drusen morphology showed a negative correlation between drusen size and disrupted IS/OS junction/photoreceptor integrity ($r = -0.37$, $p < 0.001$) at initial scanning and at follow-up visit ($r = -0.48$, $p < 0.001$). Drusen size significantly correlated with the IS/OS-junction at initial scanning for each group (group A, $r = -0.36$, $p = 0.001$; group B, $r = -0.37$, $p < 0.001$; group C $r = -0.46$, $p < 0.001$). At follow-up visit a correlation was seen for groups B ($r = -0.66$, $p < 0.001$) and C ($r = -0.41$, $p < 0.001$). The change of drusen size significantly correlated with the change of the IS/OS-junction for groups B

($r=-0.20$, $p=0.003$) and C ($r=-0.49$, $p<0.001$) over time. Table 1 shows all correlation coefficients of drusen size and IS/OS-junction grading.

Within group A there were 64 drusen (77% of all regressed drusen) that initially showed intact IS/OS junction integrity (IS/OS grading 3 and 2; 63 of those drusen (98%) demonstrated intact IS/OS junction after regression. Nineteen drusen that regressed were found to have major disruption of the IS/OS-junction (grading 0 and 1) at initial visit. Interestingly, out of the 19 drusen (19% of all regressed drusen) with disrupted IS/OS junction, 14 drusen showed mainly intact photoreceptor integrity after regression (74%). Between the three groups, a change to intact photoreceptor integrity appeared more often in the regression group than in the other groups ($p<0.001$).

Discussion

Drusen are a significant feature of dry AMD and often accompanied by RPE changes. They are clinically seen as yellow deposits and visualized in fundus photography. The use of stereo color fundus photography is a standard method for drusen grading in the AREDS studies.¹⁴ However, this method provides only minimal information about drusen, RPE and retinal layers.

In contrast to standard photography, high-speed high-resolution SD-OCT has become a more frequent and useful tool in clinical praxis. High-speed decreases motion artifacts and fixation problems, high-resolution allows to image smaller areas more precisely. This technique makes it possible to characterize single drusen ultra structure and overlying photoreceptors.¹⁵ In a previous study we have performed serial raster scans of the entire macula for drusen quantification and measuring individual drusen volume.¹¹ The use of high-speed ultra-high OCT for 3 dimensional imaging of retinal structures may improve to diagnose and monitor macular pathologies.¹⁶

This study was performed to investigate if drusen change over time shows structural changes to the overlying photoreceptor IS/OS-junction integrity. It reports about correlation of drusen evolution to structural changes of the IS/OS-junction. A total of 416 out of 2462 drusen were analyzed for progression, stabilization and disappearance using the combined SLO/SD-OCT device. Several studies imaging drusen with SD-OCT have observed hyper-reflective foci overlying drusen.^{8,17} The authors suggested that these hyper-reflective foci represent RPE cell migration. Also thinning of the photoreceptor layer overlying drusen has been reported.¹⁸ Histology underlines these observations showing changes in the photoreceptor layer over larger drusen, which included a reduction of the outer nuclear layer and changes of the synaptic cytoarchitecture.¹ Drusen induced transformation of outer retinal layers is an indicator for progression of the disease may play an important role in explaining the development of atrophy to the overlying RPE and photoreceptors.

Our data is in accordance to the previous histologic observation. We showed that the progression of drusen size increases the structural disruption of the photoreceptor IS/OS-junction integrity. However, SD-OCT does not give any histologic information about the retina and drusen overlying photoreceptors. It mainly shows different reflectivity of the IS/OS-junction. Therefore, our interpretation of IS/OS-junction disruption could also be a disorganization of the photoreceptors and not obviously cell damage.

Drusen regression and disappearance is a well-described phenomenon in early AMD.^{19,20} The recent study using color fundus photography has been demonstrating spontaneous drusen regression, however, parallel to regression, new drusen in other locations appeared and grew in size.⁷ It is believed that drusen disappearance is beneficial for the disease. Many efforts have been made to cause drusen regression using medication or laser therapy.^{21,22}

Subthreshold laser was ineffective and caused disruption of the RPE.²³ Medication therapy of a small number of drusen is still a preliminary attempt.

Spontaneous drusen regression has not been described previously using SD-OCT. A recent study demonstrated that drusen are able to break through the IS/OS junction.²⁴ We therefore hypothesized that large drusen involving the IS/OS-junction may cause visible defects to outer retinal layers after regression/disappearance.

In our study, out of the drusen that regressed two thirds disappeared completely and one third of the drusen regressed in size. However, when they disappeared in one location, new drusen appeared next to that area. It can still be discussed if the drusen just moved and shifted to the side or if new drusen grew. This is in accordance to what was seen in color photography.^{7,19} More interestingly, after drusen regression/disappearance, grading of the IS/OS-junction showed mostly intact IS/OS integrity, even of drusen with initially major IS/OS disruption. This result indicates that there is normal photoreceptor layer after drusen regression. In accordance, a study measuring retinal function did not show any difference in retinal sensitivity between retinal areas with regressed drusen compared to unaffected retinal areas.²⁵

We conclude that the drusen-induced compression of the IS/OS-junction is most probably related to a structural disruption of the IS/OS-junction over drusen that progress. In contrast, the IS/OS-junction over drusen that regress, might be artifactitiously compressed and not initially visible. We observed that the IS/OS structure changed back to normal after drusen regression/disappearance. It also might be possible for the IS/OS-junction to restore its integrity after drusen regression. However, it is very unlikely that such compression will not cause any damage to the IS/OS-junction: Yi et al. have shown that there is reduced reflectance of the boundary between the IS/OS-junction around drusen and Curcio described damage of the photoreceptor layer because of dysfunctional retinal pigment epithelium.^{26,27} Therefore, attention is needed in the grading of the photoreceptor IS/OS-junction integrity. We do believe, as imaging technology progresses, that devices with better resolution showing single photoreceptors in vivo will reveal new insight of drusen regression influence to the retina. Further investigation in the future is needed to analyze the effects of drusen regression in early AMD.

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Figure 1. Spectral domain optical coherence tomography (SD-OCT) of a druse showing height measurement using the electronic caliper from the Spectralis software.

Figure 2.

Spectral domain optical coherence tomography (SD-OCT) showing the different gradings of the inner segment/outer segment (IS/OS-junction) indicated by the arrow. (A) grade 0: the IS/OS-junction is completely disrupted or fused with the druse, (B) Grade 1 focal disruption of the IS/OS junction more than 50%, (C) Grade 2 focal disruption of the IS/OS junction less than 50%, (D) Grade 3 intact IS/OS layer.

Figure 3.

Examples of drusen imaged with spectral domain optical coherence tomography (SD-OCT) at initial time point (upper images, A1, B1, C1) and at final visit (follow-up) after a mean time of 26.3 months (lower images, A2, B2 and C2) from different subjects: drusen regression/disappearance (A), drusen without change (B) and drusen progression (C). Locations were checked manually using vascular landmarks and also by the eye tracker built into the SLO-OCT device (Spectralis)

Figure 4.

The diagram is showing the evolution of drusen height for each group (y-achsis); x-achsis: A1 total drusen regression/disappearance, A2 partial drusen regression, B drusen without change (stable), C drusen progression. The columns in dark shades are indicating mean drusen height at baseline, the columns in light shade at follow-up visit.

Figure 5.

Distribution of drusen grading at time point of follow-up, indicated in different shades, for each grade (grade 0–3): regression (A) stable (B) and progression (C). x-axis: drusen grading at baseline; y-axis: frequency of drusen. With drusen regression (A), grading of the IS/OS-junction demonstrates higher grading scores (grading 2 and 3) at time of follow-up indicating intact photoreceptor integrity. With drusen growth (C = progression) the IS/OS-junction shows lower grading scores (grading 0 and 1) at time of follow-up indicating damaged photoreceptor integrity.

Figure 6.

Infrared picture (left), spectral domain optical coherence tomography (SD-OCT; right) image of drusen in a localized area that progressed (asterix) and regressed (arrow). This example demonstrates that the inner segment/outer segment (IS/OS-junction) gets disrupted with drusen growth. The location where the druse disappeared shows complete restoration of the IS/OS-junction. The small arrow on the left is pointing a vessel as a proof of correct alignment of both SD-OCT images.

Table 1

Correlation coefficients after cross-sectional analysis of drusen size and IS/OS-junction grading of each group (regression, stable, progression) at baseline and follow-visit and their change (difference) over time. The asterix indicates statistical significance $p < 0.001$.

	Spearman correlation coefficient of drusen size and IS/OS--grading		
All	−0.37 *	−0.48 *	−0.51 *
Group A	−0.36 *	−0.27	−0.14
Group B	−0.37 *	−0.66 *	−0.20
Group C	−0.46 *	−0.41 *	−0.49 *

*
: $p < 0.001$