High-Resolution Imaging of Photoreceptors in Macular Microholes

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PURPOSE. To assess photoreceptor structure in macular microholes by using adaptive optics scanning laser ophthalmoscopy (AO-SLO) and spectral-domain optical coherence tomography (SD-OCT) and compare with visual acuity.

METHODS. Fourteen eyes from 12 patients with macular microholes underwent a full ophthalmologic examination and imaging with a fundus camera, SD-OCT, and an original prototype AO-SLO system at each visit.

RESULTS. All eyes had a cone outer segment tip line disruption and a normal retinal pigment epithelium line on SD-OCT images. Adaptive optics scanning laser ophthalmoscopy revealed foveal cone disruption (13 eyes, round or oval; 1 eye, T-shaped) in all eyes. Cone disruption area (mean = 14,805 ± 9120 μm²; range, 3495–35,901 μm²) positively correlated with logMAR visual acuity at the first visit (P = 0.015, rₛ = 0.679). During the follow-up period, cone disruption area increased in two eyes, was stable in seven eyes, and decreased in five eyes. At the last visit, cone disruption area (mean = 8717 ± 7432 μm²; range, 0–25,746 μm²) also positively correlated with logMAR visual acuity (P = 0.035, rₛ = 0.610). In one patient with bilateral microholes and no apparent vitreous traction, lesion size gradually increased. Cone disruption area decreased and visual acuity improved following oral prednisone therapy.

CONCLUSIONS. Cone disruption occurs in eyes with macular microholes and a larger cone disruption area translates into a poorer visual acuity. Macular microholes, which are commonly observed as foveal cone inner and outer segment disruptions, may occur in eyes with or without vitreofoveal traction.

Keywords: macular microhole, optical coherence tomography, adaptive optics, scanning laser ophthalmoscopy.
Medicine. The nature of this study, participation in it, and possible risks and benefits were explained to study candidates, after which written informed consent was provided by all participants.

Participants

There were a total of 14 eyes from 12 participants (five men, seven women) in this observational case series. Average patient age was 59.4 ± 11.5 years (range, 36–73 years) and all patients had macular microholes with no other macular abnormalities, glaucoma, or inherited color blindness. All participants visited the Kyoto University Hospital in Kyoto, Japan, between February 2008 and May 2012. All patients were followed for at least 12 months.

All patients were diagnosed with macular microholes, based on the presence of a demarcated, red, intraretinal, foveal, or juxtafoveal defect. Patients with a full-thickness macular hole (MH), solar retinopathy (including history of visual disturbance after sun gazing), laser pointer burn, any toxic maculopathy, history of trauma, amyl nitrate abuse, welding arc maculopathy, lightning maculopathy, cone dystrophy, and occult macular dystrophy were excluded from participation. Eyes with high myopia (axial length > 26.5 mm) were also excluded.

Ophthalmologic Examinations

All participants underwent comprehensive ophthalmologic examinations at baseline, which included measurement of best-corrected visual acuity (BCVA), intraocular pressure (IOP), and axial length (IOLMaster; Carl Zeiss Meditec, Dublin, CA, USA). Measurement of BCVA was performed using the Landolt chart and expressed as logMAR. In addition, indirect ophthalmoscopy was performed at each follow-up visit, all participants underwent BCVA measurement, fundus photography, SD-OCT, and AO-SLO.

Spectral-Domain Optical Coherence Tomography

Examinations with SD-OCT were performed in all eyes using a commercial device (Spectralis HRA+OCT; Heidelberg Engineering, Dossenheim, Germany). Horizontal and vertical line scans through the center of the fovea were obtained at a 30° angle, after which we performed 12 radial scans centered on the fovea. We then obtained volume scans (horizontal B-scans at 10° × 30°). At each location of interest on the retina, 50 SD-OCT images were acquired and averaged to reduce speckle noise.

The reflectivity of the inner segment/outer segment (IS/OS) or cone outer segment tip (COST) was measured from within a 40-μm slab, and the IS/OS or COST line was quantified by using the plot profile function of ImageJ software (http://image.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) with a 6-pixel fixed-width line. The border of the IS/OS or COST disruption was defined as the line on the grayscale image along which the IS/OS or COST reflectivity diminished by 2 SD from the reflectivity of the IS/OS or COST line in the unaffected retina.

Outer nuclear layer (ONL) thickness was measured at the center of the fovea. Foveal ONL thickness was defined as the distance between the vitreoretinal interface and the external limiting membrane. We have also measured the ONL + outer plexiform layer (OPL) thickness 0.5 and 1.0 mm from the center of the fovea.

Prototype AO-SLO

Our AO-SLO system has been previously described in full. Briefly, the AO-SLO system used in this study was designed and constructed in our laboratory, based on previous reports of how incorporating a wide-field SLO is useful. The AO-SLO system is confocal, allowing it to create high-contrast “en face” images in any plane. The system is composed of four primary optical subsystems: the AO subsystem (wavefront sensor, spatial light modulator), the high-resolution confocal SLO imaging subsystem, the wide-field imaging subsystem, and the pupil observation subsystem. The pupil subsystem facilitates initial pupil alignment with the AO-SLO system’s.
optical axis through chin rest position adjustment. The wavefront sensor measures aberrations in the eye as a whole, and the spatial light modulator compensates for these aberrations. The total acquisition time was 10 minutes for one eye.

**Cone Mosaic Imaging With the AO-SLO**

A series of AO-SLO images was acquired at each of several macular locations by shifting the focal point from the retinal nerve fiber layer to the RPE, with particular attention paid to acquiring images showing the cone mosaic. We automatically created a montage of AO-SLO images by using MosaicJ (National Institutes of Health, Bethesda, MD, USA). If necessary, we made manual corrections by selecting both the area of interest and each image to be included in the montage. Proper reconstructions of AO-SLO images were verified by comparing the final montage to the corresponding wide-field images for that eye. The postprocessing time was 30 minutes for each image.

The size of the dark lesion in each eye was quantified in AO-SLO images by two independent, experienced examiners using ImageJ software, a Java-based image-processing software program (Fig. 1). In ImageJ, the command path of ImageJ >

**Table 1. Clinical Data of Patients With Macular Microholes**

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<th>Eye</th>
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<th>BCVA Last Visit</th>
<th>Vitreous Condition</th>
<th>OPL/ONL, μm*</th>
<th>OPL/ONL, μm†</th>
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<td>L</td>
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<td>20/20</td>
<td>VFS</td>
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<td>91</td>
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OPL/ONL, thickness of outer plexiform layer and outer nuclear layer.

* 1.0 mm temporal from the center of the fovea.
† 0.5 mm temporal from the center of the fovea.
‡ 0.5 mm nasal from the center of the fovea.
§ 1.0 mm nasal from the center of the fovea.

**Figure 2.** Unilateral macular microhole with vitreofoveal separation. Images from the left eye of a 58-year-old man with a macular microhole (case 3). Best-corrected visual acuity was 20/20. (A) Fundus photograph showing a small, faint, irregular, red lesion at the foveal center (arrow). (B) High-magnification view of the foveal center. (C) Infrared image. (D) Spectral-domain optical coherence tomography image. Horizontal line scan through the foveal center, taken in the direction of the arrow in (C). Small outer retinal defects, selective thinning of the outer nuclear layer in the fovea, and a vitreofoveal separation (green arrowbeads) are visible.
FIGURE 3. Magnified SD-OCT and AO-SLO images of the fovea (case 3). (A) The SD-OCT revealed photoreceptor IS/OS junction line and COST line defects at the fovea (blue arrowhead). The retinal pigment epithelial line was intact. The adaptive optics-SLO images show dark regions, representing cone disruption. (B) Three years later, dark area was almost stable. Scale bar: 100 μm.

TABLE 1. Extended

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<th>ONL Fovea, μm</th>
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<th>OPL/ONL, μm§</th>
<th>COST Disruption</th>
<th>Hyperreflective Lesion</th>
<th>Cone Loss Area First Visit, μm²</th>
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Adjust > Threshold was used to differentiate the dark area from the nondark area. Brightness was adjusted manually by the grader. To measure the dark area, the command path of Analyze > Measure was used. To obtain accurate scan lengths, the magnification effect in each eye was corrected using the adjusted axial length method, previously devised by Bennett et al.38

To evaluate cone density, we applied the automated cone labeling process of Li and Roorda. 39 After automated cone labeling, an experienced observer examined each image. The area for quantification (80 × 80 μm) was identified manually by selecting the area without vascular shadows and by placing the computer cursor on the area to be quantified. This method has been used in other studies.19,24,25,26,28,33 As has been reported for similar systems, 6–28 we found that our system did not always allow clear visualization of individual cones within much of the central fovea. However, we could clearly distinguish individual cones ≥ 0.5 mm from the center of the fovea. Therefore, we obtained an estimate of cone density in areas 0.5 mm from the foveal center by dividing the number of cones in each imaging area by the size of the area. We measured cone density in each of four directions (superior, lower, nasal, and temporal), and the mean density was calculated from the densities in all four directions.

Statistical Analyses

Statistical analysis was done using only one eye per patient. We used the data of the right eye in bilaterally affected cases. For intraobserver measurements, one-way random, average measure intraclass correlation coefficients (ICC) were obtained. Wilcoxon signed tests were used to compare parameters between the first and last clinic visits. The Spearman rank correlation coefficient was calculated to examine the association between cone disruption area and logMAR BCVA. All statistical calculations were performed using a commercially available statistical software program (SPSS, version 17; SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as P < 0.05.

RESULTS

Participant clinical characteristics are summarized in Table 1. Fourteen eyes from 12 patients (five men, seven women) were included in this observational case series. Mean participant age was 59.4 ± 11.5 years (range, 36–73 years) and mean logMAR BCVA was 0.082 ± 0.087 (range, 20/12 to 20/25) at the first visit. At the last visit, on average 26.9 ± 11.4 months (range, 12–44 months) later, mean logMAR BCVA was −0.041 ± 0.081 (range, 20/12 to 20/30), which was no different from the first visit (P = 0.097).

A small, red, well-demarcated, intraretinal, foveal defect was seen in all eyes (Figs. 2–9, Supplementary Figs. S1, S2). Three eyes (21%) had a complete posterior vitreous detachment (PVD) and 6 eyes (43%) had a vitreofoveal separation (VFS, Fig. 2). The two participants with bilateral macular microholes and one patient with a unilateral microhole did not have a PVD, a VFS, or vitreous traction (Figs. 4, 7).

All 14 eyes had a disruption of the IS/OS and COST line on SD-OCT images and a normal RPE line (Figs. 2–5, 7–9, Supplementary Figs. S1, S2). Additionally, three eyes with
VFS also had a moderately reflective lesion in the outer nuclear layer (ONL, Fig. 3). The mean ONL thickness of the fovea was 86.2 ± 17.9 μm (Table 2).

Foveal dark lesion was observed in all 14 eyes on AO-SLO. In 13 eyes, the lesion was round or oval (Figs. 1, 5, 6, 8, 9, Supplementary Fig. S2) and in 1 eye it was T-shaped (Fig. 3). Cone abnormalities were limited to the fovea in all eyes (Fig. 6). The reproducibility of the dark area measurements was evaluated through an interobserver ICC. The ICC was 0.944 for measurement at the first visit and 0.952 at the last visit. The 95% confidential intervals for ICC values were 0.834 to 0.982 at the first visit, and 0.858 to 0.984 at the last visit.

The IS/OS and COST disruption size on SD-OCT correlated with the dark area on AO-SLO ($P = 0.006$, $r_s = 0.741$ and $P = 0.003$, $r_s = 0.776$, respectively) at the first visit. The IS/OS and COST disruption size correlated with the dark area on AO-SLO ($P = 0.005$, $r_s = 0.749$ and $P < 0.001$, $r_s = 0.858$, respectively) at the last visit as well.

Cone disruption area (mean = 14,805 ± 9120 μm$^2$, range, 3495-35,901 μm$^2$) positively correlated with logMAR visual acuity at the first visit ($P = 0.015$, $r_s = 0.679$). The dark area increased by >20% in two eyes (14%), was stable in seven eyes (50%), and decreased by >20% in five eyes (36%). Three eyes showed complete resolution of cone disruption (Supplemen-

![Figure 5](image-url) Magnified SD-OCT and AO-SLO images of the fovea (case 10, right eye). (A) The SD-OCT image showed COST line defects and an irregular IS/OS line at the foveal center (blue arrowhead). The retinal pigment epithelial line was intact. The adaptive optics-SLO images show dark, round regions, representing central foveal cone disruption. (B) Two years later, the size and shape dark regions was almost stable. Scale bar: 100 μm.

![Figure 6](image-url) Montage AO-SLO images of the fovea and parafovea (case 10, right eye). Right: High-magnification views of the areas outlined by the white boxes. Note that cone mosaic is normal except for the center of the fovea. Scale bar: 100 μm.
Of the 5 eyes where cone disruption decreased during the follow-up period, three had a VFS and two had a complete PVD. Interestingly, the dark area was either stable or decreased in all eyes with a VFS or a complete PVD. At the last visit, cone disruption area (mean $= 8717 \pm 7432$ lm$^2$; range, 0–25,746 lm$^2$) also positively correlated with logMAR visual acuity ($P = 0.035, r_s = 0.610$). The mean cone density 0.5 mm from the center of the fovea (i.e., the area around the lesion) was 31,812 $\pm$ 2715 at the first visit and 31,664 $\pm$ 2515 at the last visit ($P = 0.583$; Table 2), which was within normal range.$^{19,25,26,28}$

Five eyes (36%) had no apparent signs of either past or present vitreous traction. In one 36-year-old participant with bilateral microholes and no evident vitreous traction, retinal lesion size gradually increased. Unfortunately, the patient also experienced a gradual increase in scotoma size. Treatment with oral prednisone (40 mg/d) was initiated 16 weeks after the initial visit to prevent further cone disruption, and subsequent vision loss. With systemic steroid treatment, dark area decreased and visual acuity improved (Figs. 8, 9).

**DISCUSSION**

Macular microholes are diagnosed based on the presence of a red, well-demarcated, intraretinal, foveal, or juxtafoveal defect on fundoscopic examinations or fundus photography.$^1$–$^5$ However, the lesion is usually very small, and the disease may be easily overlooked during standard fundoscopic examinations. Although SD-OCT is more sensitive than AO-SLO generally, macular microholes may even be overlooked on SD-OCT images without dense B-scans. The intervals of each B-scan are more than 20 lm, even using a raster scan, with lateral resolution of $\sim 20$ lm, whereas the AO-SLO, with lateral resolution of 3 lm, can detect $\sim 20$-lm-wide abnormalities. In fact, the dynamic lesion changes were more apparent on AO-SLO images than on SD-OCT images (Figs. 8, 9). Thus, the combination of fundus examination, SD-OCT, and AO-SLO may be useful in accurately diagnosing macular microholes and for monitoring patients with the disease. Recently Flatter et al.$^{40}$ reported the SD-OCT and AO-SLO findings of photoreceptor damage after blunt trauma, which are similar to those of...
macular microholes. In both conditions, the lesions were very small, and AO-SLO is useful for evaluating and monitoring patients.

We propose that the “dark area” on AO-SLO represents abnormalities at the photoreceptor level. This proposal is based on several findings. First, foveal ONL thickness was smaller in eyes with macular microholes (86 ± 18 μm), compared with normal eyes (122 ± 23 μm). Second, a comparison of AO-SLO images with wide-field SLO images or fundus photographs allowed us to rule out the possibility that the dark areas represented the shadows of blood vessels. Moderately reflective foveal lesions (Fig. 3) seem to have little effect on the penetration of light reflected from the deeper layers. In fact, on SD-OCT, which uses a light source with a wavelength (840 nm) identical to that of our AO-SLO system, no shadows were observed in the photoreceptor layer or RPE.

Third, the dark areas on AO-SLO positively correlated with the areas of disruption in the IS/OS and COST line on SD-OCT images.

Recently, Spaide and Curcio hypothesized that the IS/OS lines and COST lines correspond to the ellipsoid zone of the photoreceptors and the contact cylinder of the cones. The ellipsoid section is a part of the photoreceptor inner segments and is densely packed with mitochondria. The OS continues to the RPE, whereupon it is enveloped in specialized apical processes, forming a contact cylinder. Thus, it is possible that the appearance of the presumed IS/OS line reflects the function of the photoreceptor inner segments, and the appearance of the presumed COST line reflects the function of the photoreceptor outer segments. The high reflectance of
the cone mosaic in AO-SLO is thought to be caused by reflectance from both the IS/OS and the COST in the normal retina. In fact, the current study showed that the dark area was correlated with larger decreases in the reflectivity sizes of the IS/OS and COST. However, dark areas were also observed on AO-SLO images in the areas where the IS/OS line was continuous (though it was irregular), but the COST line was disrupted, on SD-OCT (Figs. 7–9). This finding is consistent with the results of a study by Kitaguchi et al., in which the dark area observed on AO fundus camera images corresponded with the areas where the COST line, rather than the IS/OS, was disrupted on SD-OCT images. Thus, the OS probably plays a more important role in the reflectance of the photoreceptor mosaic on AO-imaging devices. This is also supported by the recent split detector AO-SLO imaging performed by Scoles et al.

Previous studies examining OCT images of macular microholes have revealed retinal structural abnormalities. Using time-domain OCT, Zambarakji et al. found an outer retinal abnormality and/or RPE defect on many OCT series. Using SD-OCT, Gella et al. also reported the presence of photoreceptor layer abnormalities in all OCT series, with some eyes also having RPE abnormalities. However, both studies used single, and not averaged, images so speckle noise likely limited detailed layer analyses. In the current study, the speckle-noise-reduction capabilities of the SD-OCT device (eye tracking combined with multiple B-scan averaging, Spectralis; Heidelberg Engineering) allowed us to obtain highly detailed images of all retinal layers. Disruptions of the IS/OS and COST line were found in all eyes examined, and the RPE line was normal. In addition, AO-SLO revealed dark area in the fovea in all eyes. Thus, the current study shows that foveal cones, especially the

**FIGURE 9.** Resolving bilateral macular microholes after oral prednisone. Magnified SD-OCT and AO-SLO images from case 11. Treatment with oral prednisone (40 mg/d) 16 weeks after the initial visit prevented further vision loss (BCVA: 20/32 in the right eye, 20/25 in the left eye). By the last visit, the cone disruption region size had decreased and visual acuity had subsequently improved (BCVA: 20/20 in the right eye, 20/16 in the left eye). Note that the dynamic lesion changes are more apparent on AO-SLO images than in SD-OCT images. Scale bar: 100 μm.
gradual recovery of the IS/OS line in closed full-thickness macular hole. This phenomenon may be consistent with the photoreceptor cell body and the inner segment remaining stable or decreased in all eyes with VFS or a complete PVD, both of which are evidence of past anteroposterior vitreous traction at the macula.2,4,5 In the current study, nine eyes (64%) had evidence of acute or prior vitreous traction (i.e., VFS, complete PVD) on the fovea. This led us to hypothesize that, when a certain kind of macular microhole forms, cone photoreceptors are pulled away from the RPE, as a result of anteroposterior traction on the photoreceptor layer, which is mostly made up of cones in the fovea. We believe that this traction is caused by posterior vitreous traction or acute detachment of vitreous.

Lai et al.44 examined spontaneous resolution of macular microholes and found that a type of macular microhole can form while a full-thickness macular hole is resolving. Histopathologic studies of repaired full-thickness macular hole have shown that photoreceptor cells are replaced by Müller cells and/or astrocytes at the site of the macular hole.45–47 These cellular changes may explain the moderately reflective ONL lesions seen on OCT that were first reported by Ko et al.48 on ultrahigh-resolution OCT images. In the current study, three eyes with macular microholes, all of which had VFS, had these moderately reflective ONL lesions in the macula. Together, this evidence suggests that these eyes may have had a resolving full-thickness macular hole.

During the follow-up period (26.9 months on average), the dark area was stable or decreased in all eyes with VFS or a complete PVD, both of which are evidence of past anteroposterior vitreous traction on the macula, may spontaneously decrease in size once the traction is no longer present. Additionally, if the photoreceptor cell body and the inner segment remain intact, the cell will regenerate its outer segment and visual acuity improves. This phenomenon may be consistent with the gradual recovery of the IS/OS line in closed full-thickness macular hole after vitreous surgery.49–51

Five eyes (36%) had no apparent signs of either past or present vitreous traction. Thus, macular microholes may be divided into at least two subtypes, based on the involvement of anteroposterior vitreous traction. The pathology of macular microholes without the involvement of anteroposterior vitreous traction may be similar to that of acute zonal occult outer retinopathy (AZOOR) complex disease, in which disruptions of the IS/OS and the COST lines are the characteristic findings on OCT as well.52–55 Indeed, in one middle-aged patient with bilateral microholes, lesion size gradually increased with no apparent vitreous traction. When the size of cone disruption regions decreased following oral steroid therapy, visual acuity also improved, which is similar to the report of Spaide et al.53 that oral steroid and immunosuppressants reconstituted IS/OS line defects in eyes with AZOOR complex disease. Although macular microholes caused by acute anteroposterior vitreous traction are photoreceptor defects secondary to vitreofoveal traction, this microhole subtype may be caused by the primary damage of the photoreceptor outer segments.

In the current study, a larger dark area in the fovea on AO-SLO coincided with a worse visual acuity at both the first and last clinic visit. This pattern is consistent with a previous report using SD-OCT and microperimetry techniques, which found correlations between the macular microhole size and the retinal sensitivity reduction.5 Cumulatively, these findings suggest that macular functional impairment is closely associated with foveal cone photoreceptor changes in eyes with macular microholes.

Our study has several limitations. First, this study examined a relatively few eyes due to practical limitations associated with the rarity of macular microholes. Second, although it has better lateral resolution than commercially available SD-OCT, our AO imaging equipment was unable to clearly show individual cone photoreceptors near the foveal center. However, each dark area, representing cone disruption, was larger than the diameter of a single central foveal cone. In fact, cone disruption area was detectable near the foveal center, even though individual cones could not be imaged in the same location. Despite these limitations, our study shows that the combination of fundus examination, SD-OCT, and AO-SLO may be useful in diagnosing and monitoring macular microholes. Using these images, we were able to associate photoreceptor and visual acuity changes in eyes with macular microholes. Macular microholes, which are commonly observed as inner and outer segment disruptions in the fovea, may occur in cases with and without vitreofoveal traction.

References
Photoreceptor Imaging in Macular Microholes


