Regeneration of Photoreceptor Outer Segments After Scleral Buckling Surgery for Rhegmatogenous Retinal Detachment

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• PURPOSE: To investigate the regeneration of the cone outer segments in eyes after surgery for fovea-off rhegmatogenous retinal detachment with an adaptive optics (AO) fundus camera and to correlate these findings with the findings of optical coherence tomography (OCT).

• DESIGN: Retrospective, observational case series.

• METHODS: Medical charts of 21 eyes of 21 patients who had undergone surgery for fovea-off rhegmatogenous retinal detachment were retrospectively studied. Cone mosaic images were obtained with an AO fundus camera. Cone packing density at 2 degrees from the fovea within the previously detached area was measured 6 and 12 months after surgery. Retinal thicknesses between the interdigitation zone and the retinal pigment epithelium (IZ-RPE) and between the ellipsoid zone and the retinal pigment epithelium (EZ-RPE) were measured in OCT images.

• RESULTS: Cone density 12 months after surgery was significantly increased from that at 6 months (P = .001), but was still significantly lower than that of normal fellow eyes (P < .001). IZ-RPE and EZ-RPE thickness significantly increased from 6 to 12 months (P = .045, P = .033, respectively), and these values were not significantly different from those of normal fellow eyes. Multivariate analysis showed that cone density at 12 months was significantly associated with IZ-RPE thickness (P = .002), and increases in cone packing density were significantly associated with increases in IZ-RPE thickness (P = .001).

• CONCLUSIONS: Recovery of cone packing density measured by AO was associated with structural recovery of the outer retina observed in OCT, suggesting regeneration of the photoreceptor outer segment after surgery. (Am J Ophthalmol 2017;177:17–26. © 2017 Elsevier Inc. All rights reserved.)

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RHEGMATOGENOUS RETINAL DETACHMENT IS A vision-threatening disease. Scleral buckling surgery, pars plana vitrectomy, or pneumatic retinopexy can be performed to reattach the retina. Although the rate of reattachment after surgery is high, visual recovery is not always good.[1–10]

Damage of the retinal outer layers is reported to be associated with poor vision in eyes with rhegmatogenous retinal detachment. Loss of the outer segments of the photoreceptor cells has been observed in experimental studies of retinal detachment.[11–15] Recent optical coherence tomographic (OCT) studies have shown that disruptions of the external limiting membrane (ELM), ellipsoid zone (EZ), and cone interdigitation zone (IZ) of the photoreceptors are correlated with visual acuity after surgery.[7,8,16–23] Other studies have shown that restoration of the EZ of the photoreceptor and thickening of the fovea are associated with recovery of best-corrected visual acuity (BCVA) after reattachment of a rhegmatogenous retinal detachment.[8,23,24] These results suggest that the recovery of retinal function after retinal reattachment depends on the degree of regeneration of the outer photoreceptor layer.

Although OCT can show the fine structure of the retinal layers, it cannot resolve individual cone cells. The adaptive optics (AO) fundus camera or the AO scanning laser ophthalmoscope (AO-SLO) allows direct visualization of the living retina at a microscopic resolution and can distinguish individual macular cone cells and measure cone density. The AO fundus camera rtx1 (Imagine Eyes, Orsay, France) is currently approved and commercially available for clinical use in the European Union, Japan, and Australia. In the United States, the rtx1 has not received Food and Drug Administration (FDA) clearance and requires Institutional Review Board (IRB) approval for use in any research application. Measurement of cone density has good reproducibility; intraclass and interclass correlation coefficient was reported to be 0.96 and 0.98, respectively.[25] AO-SLO has not become commercially available in any countries and prototype AO-SLO has been used for the clinical research.

Using an AO fundus camera, Saleh and associates reported decreased cone density in eyes with rhegmatogenous retinal detachment 6 weeks after vitrectomy and a high correlation between cone density and postoperative

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visual acuity.[26] However, long-term changes in cone density after surgery have not been reported.

The purpose of this study was to investigate long-term cone regeneration using AO in eyes operated for rhegmatogenous retinal detachment and to correlate the findings with those from OCT.

METHODS

• **ETHICS APPROVAL AND INFORMED CONSENT:** The protocol for this retrospective observational case series study was approved by the Institutional Review Board of Nagoya University School of Medicine, and the procedures used conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients after they were provided with information on the procedures to be used.

• **SUBJECTS:** We retrospectively reviewed the medical records of 21 eyes of 21 patients (mean ± standard deviation [SD] age, 37.2 ± 13.2 years; 13 men and 8 women) who underwent a single successful unilateral scleral buckling surgery for macula-off rhegmatogenous retinal detachment and postoperative examination of AO fundus camera between November 1, 2011 and January 31, 2015 at the Nagoya University Hospital.

• **EXCLUSION CRITERIA:** Eyes with persistent subretinal fluid, macular edema, epiretinal membrane, macular fold, media opacities, or proliferative vitreoretinopathy grade ≥C[27] were excluded, because these factors decrease the image quality of cone cells. OCT images with image quality less than 15 dB were excluded to improve accuracy of the thickness measurement.

• **EXAMINATIONS:** All patients underwent comprehensive ophthalmologic examinations, including fundus examinations with indirect ophthalmoscopy, slit-lamp biomicroscopy, spectral-domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), measurement of BCVA, intraocular pressure with a noncontact tonometer (NT-530P; Nidek, Gamagori, Japan), refractive error (spherical equivalent) (KR-8900 auto Kerato-Refractometer; Topcon, Tokyo, Japan), and axial length (IOLMaster; Carl Zeiss Meditec, Dublin, California, USA).

• **SURGICAL TECHNIQUE:** All patients underwent a single successful unilateral scleral buckling surgery with cryopexy. During the surgery subretinal fluid was drained, and gas tamponade was not used. All patients had a complete retinal reattachment after the initial operation. All surgeries were performed on the day of diagnosis or 1 day after.

• **ADAPTIVE OPTICS SYSTEM AND IMAGE ANALYSIS:** AO images taken approximately 6 and 12 months (188.1 ± 32.1 days and 369.6 ± 34.9 days, respectively) after surgery were analyzed using the AO fundus camera (rtx1; Imagine Eyes). The details of the rtx1 AO camera are described elsewhere.[28] Images of the fovea and the macular area 2 degrees nasal, temporal, superior, and inferior from the fovea were obtained. In one of these locations, the cone packing density at 2 degrees from the foveal center within the previously detached area, and at the same area in the fellow eyes, were measured with the use of a proprietary software (AO Detect; Imagine Eyes). The area of previous detachment was identified in the Spectralis fundus images and AO analysis was performed for the detached area. In the analysis, cone cells were automatically detected and manually corrected for the analysis, and cone density was automatically calculated in cells/mm^2 by the proprietary software.

• **SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY MEASUREMENTS:** For the Spectralis OCT images, radial scans with 30-degree angle were performed. In each image, 100 OCT scans were averaged for each OCT image with the use of the eye-tracking system.

In the preoperative OCT image, total retinal thickness (from the internal limiting membrane to the EZ) and height of retinal detachment was measured at the corresponding area of AO (2 degrees from the foveal center). The thickness of the retina from the EZ to the outer border of the detached retina was not included because it was difficult to determine the outer border owing to its irregular shape.

In the OCT images, 4 outer retinal lines are often seen in high-quality OCT images: ELM, EZ, IZ, and retinal pigment epithelium (RPE). In the postoperative OCT images, we chose to measure the following parameters: thickness of retina between the ELM and the EZ (ELM-EZ, ie, the inner segment thickness), between the EZ and the IZ (EZ-IZ, ie, the outer segment thickness), and between the IZ and the RPE (IZ-RPE, ie, the thickness of the cone sheaths), and the thickness of the outer nuclear layer (ONL) at corresponding areas of AO in both eyes, because they have been correlated with outer segment structures and health (Figure 1).

When the thickness of the retinal layer, including the EZ, the IZ, or the ELM, was measured, the existence of the line was judged by the previously proposed method,[29] which used ImageJ software (National Institutes of Health, Bethesda, Maryland, USA) (Figure 2). In brief, a vertical line with 100-μm thickness was drawn at the selected location, and if the intensity of the EZ line was more than 60% of the intensity of the RPE, the EZ line was judged to be present. If the intensity of the IZ line was more than 80% of that of the RPE, the IZ line was judged to be present. If the intensity of the ELM line was more than 20% of that of the RPE, the ELM line was judged to be present.[29] The thickness of the outer layers was measured at the peak of intensity. In eyes without IZ, IZ-RPE thickness was calculated as 0 μm.

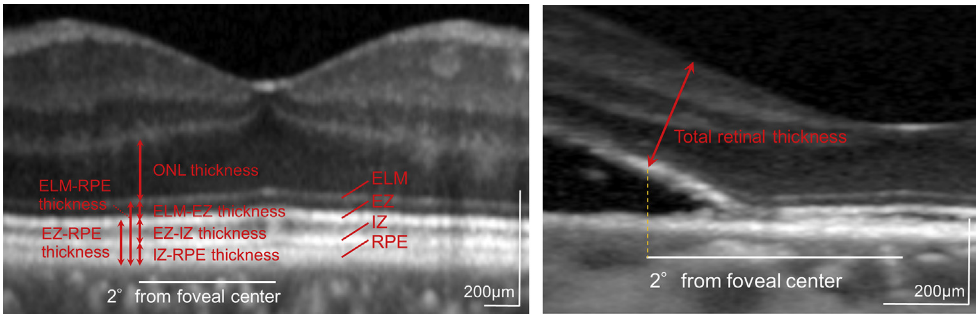

FIGURE 1. Representative optical coherence tomography (OCT) images. (Left) The thickness between the interdigitation zone (IZ) and the retinal pigment epithelium (RPE) (IZ-RPE), the thickness between the ellipsoid zone (EZ) and the RPE (EZ-RPE), the thickness between the external limiting membrane (ELM) and the RPE (ELM-RPE), the thickness between the ELM and the EZ (ELM-EZ), the thickness between the EZ and the IZ (EZ-IZ), and the thickness of the outer nuclear layer (ONL) at 2 degrees from the fovea were measured. (Right) Total retinal thickness between the internal limiting membrane and the EZ at 2 degrees from the fovea in the preoperative image was measured.

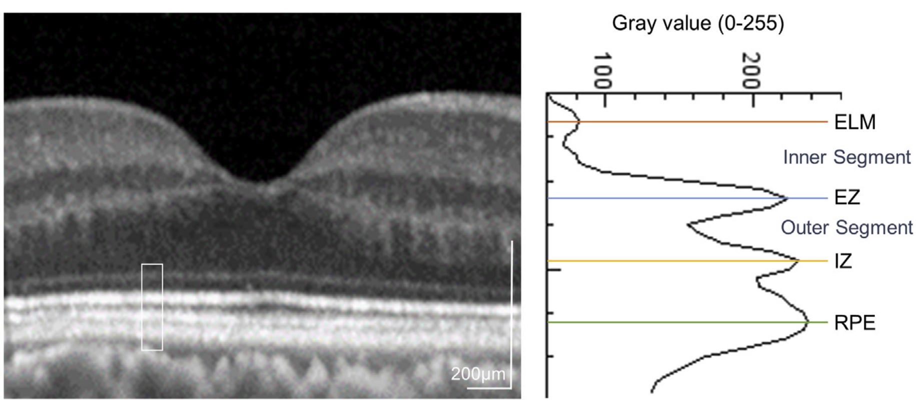

FIGURE 2. Methods of determining the existence of the ellipsoid zone (EZ), interdigitation zone (IZ), and ELM, and locating the EZ, IZ, external limiting membrane (ELM), and retinal pigment epithelium (RPE). (Left) In the ImageJ software, a 100-μm-thick line was drawn vertically in the outer retina. (Right) The intensity profile was obtained. The EZ line was judged to be present if the intensity of the peak of the EZ was more than 60% of the intensity of the RPE. The IZ line was judged to be present if the intensity of the peak of the IZ was more than 80% of the intensity of the RPE. The ELM line was judged to be present if the intensity of the peak of the ELM was more than 20% of the intensity of the RPE.

• **REPRODUCIBILITY:** The reproducibility of cone density measurements was determined with intra- and intergrader interclass correlation coefficients (ICCs). Cone density was measured twice by a single grader in 10 randomly selected AO images of 5 eyes with retinal detachment and 5 fellow eyes of retinal detachment for the intragrader ICCs. For the intergrader ICCs, each AO image was independently measured by 2 graders. For both measurements, the graders were masked to the clinical characteristics of the subjects, such as age, sex, or with or without retinal detachment.

• **STATISTICAL ANALYSIS:** One-way analysis of variance with Tukey post hoc test was used to evaluate changes in BCVA, retinal layer thickness, and mean cone packing density. Pearson correlation coefficient was used to evaluate the association between them. Univariate and multivariate regression analysis were used to find the OCT thickness parameters most associated with cone packing density after surgery. $P < .05$ was considered to indicate statistical significance. Data were analyzed using SPSS Statistics 23.0 (IBM, Somers, New York, USA).

RESULTS

THE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF the 21 patients are shown in Table 1. The detached retina was successfully reattached in a single surgery in all cases. The fovea was detached in all eyes, but the macular area was partially detached with the involvement of the fovea in 15 eyes (71%) and totally detached in 6 eyes (29%).

TABLE 1. Summary of Retinal Detachment Patient Characteristics

Characteristics	Value
Number of patients/eyes	21/21
Male/female, n (%)	13 (62)/8 (38)
Age (y), mean ± SD	37.19 ± 13.2
BCVA (logMAR), mean ± SD	
Preoperative	0.43 ± 0.54
Postoperative 6 months	0.10 ± 0.17
Postoperative 12 months	0.07 ± 0.17
Axial length (mm), mean ± SD	
Affected eye	25.76 ± 1.11
Fellow eye	25.78 ± 1.09
Duration of symptom (d), median (IQR)	4 (2–7)
Involved area (quadrant), mean ± SD	1.52 ± 0.73
Cone density (cones/mm^2), mean ± SE	
Postoperative 6 months (15 eyes)	7188.0 ± 1782.2
Postoperative 12 months (21 eyes)	13 210.1 ± 1243.1
Fellow eye (21 eyes)	20 866.3 ± 440.0

BCVA = best-corrected visual acuity; IQR = interquartile range; logMAR = logarithm of the minimal angle of resolution; RD = retinal detachment; SD = standard deviation; SE = standard error.

BCVA was significantly improved at 6 and 12 months after surgery (P = .009 and P = .04, respectively), and BCVA at 12 months was not significantly different from that in the fellow eyes (P = .87).

• **ADAPTIVE OPTICS ANALYSIS:** Representative AO images are shown in Figure 3. AO images were available for 15 eyes (71%) at 6 months after surgery and for all 21 eyes at 12 months after surgery. In 15 eyes for which cone density at both 6 and 12 months after surgery were available, the mean ± standard error (SE) cone density was 7188 ± 1782 cells/mm^2 at 6 months after surgery and 13 005 ± 1656 cells/mm^2 at 12 months after surgery, a significant increase from the value at 6 months (P = .001). The mean ± SE cone density of the fellow eyes was 21 157 ± 517 cells/mm^2, significantly larger than the cone density 6 and 12 months after surgery (both P < .001) (Figure 4). In all 21 eyes, cone density at 12 months after surgery was 13 210 ± 1243 cells/mm^2 and the cone density of the fellow eyes was 20 866 ± 440 cells/mm^2.

• **OPTICAL COHERENCE TOMOGRAPHY ANALYSIS:** Table 2 shows the postoperative parameters of outer layer thickness. IZ-RPE thickness at 12 months after surgery was 28.7 ± 12.3 μm; this value was significantly greater than that at 6 months after surgery (21.0 ± 16.0 μm; P = .045) and was not significantly different from that in the fellow eyes (33.6 ± 2.7 μm; P = .41). EZ-RPE thickness at 12 months after surgery was 57.6 ± 4.1 μm; this value was significantly greater than that at 6 months after surgery (46.8 ± 22.0 μm; P = .033) and was not significantly different from that in the fellow eyes (62.5 ± 2.7 μm; P = .42). ELM-RPE thickness at 12 months after surgery was 87.0 ± 4.3 μm; this value was significantly greater than that at 6 months after surgery (83.6 ± 5.0 μm; P = .054) and was not significantly different from that in the fellow eyes (90.0 ± 4.1 μm; P = .082). There were no significant differences in ONL, ELM-EZ, and EZ-IZ thickness between 6 months and 12 months after surgery and fellow eyes (P = .17, P = .36, P = .18, respectively).

In OCT images, EZ was present in 17 eyes (85%) 6 months after surgery and in all eyes (100%) 12 months after surgery. IZ was present in 11 eyes (55%) 6 months after surgery and in 15 eyes (71%) 12 months after surgery. ELM was present in all eyes (100%) both 6 and 12 months after surgery. Cone density was significantly greater in eyes in which IZ was present than in eyes in which IZ was not present at 6 and 12 months after surgery (9600.1 ± 1962.3 cells/mm^2 vs 555.0 ± 537.8 cells/mm^2 at 6 months; 15 944 ± 880 cells/mm^2 vs 6375 ± 1771 cells/mm^2 at 12 months; both P < .001). ELM-RPE thickness at 12 months from surgery was significantly thicker in eyes in which IZ was present than in eyes in which IZ was not present (88.3 ± 4.1 μm vs 83.7 ± 3.1 μm; P = .02). There were no significant differences of cone density between eyes with and without IZ in ONL, ELM-EZ, or EZ-RPE thickness (Table 3).

In the preoperative OCT images, total retinal thickness at the measurement point was 329.8 ± 68.0 μm and significantly correlated with postoperative cone density (6 months: P = .004; 12 months: P = .018). The mean (± SD) height of retinal detachment at the measurement point was 246.6 ± 265.6 μm. There was no significant correlation between the height of the retinal detachment and postoperative cone density (6 months: P = .302; 12 months: P = .270).

• **REGRESSION ANALYSIS:** Univariate analysis showed that cone density 6 months after surgery was significantly associated with IZ-RPE thickness (R = 0.80, P < .001), EZ-RPE thickness (R = 0.58, P = .029), and ELM-RPE thickness (R = 0.64, P < .015), and cone density 12 months after surgery was significantly associated with IZ-RPE thickness (R = 0.64, P = .002) and ELM-RPE thickness (R = 0.63, P = .002). Cone density 6 months after surgery was not significantly associated with duration of symptoms (P = .285), but cone density 12 months after surgery was significantly associated with duration of symptoms (R = 0.44, P = .048). Cone density was not significantly associated with BCVA at either 6 or 12 months after surgery (P = .68 and P = .59, respectively).

Stepwise multivariate regression analysis showed that the preoperative OCT parameter most associated with cone density at 12 months after surgery was the total retinal thickness (standardized B = 0.552; B = 49.241; 95% confidence interval [CI], 9.818–88.665; P = .018) (Figure 5, Top). The postoperative OCT parameter most associated

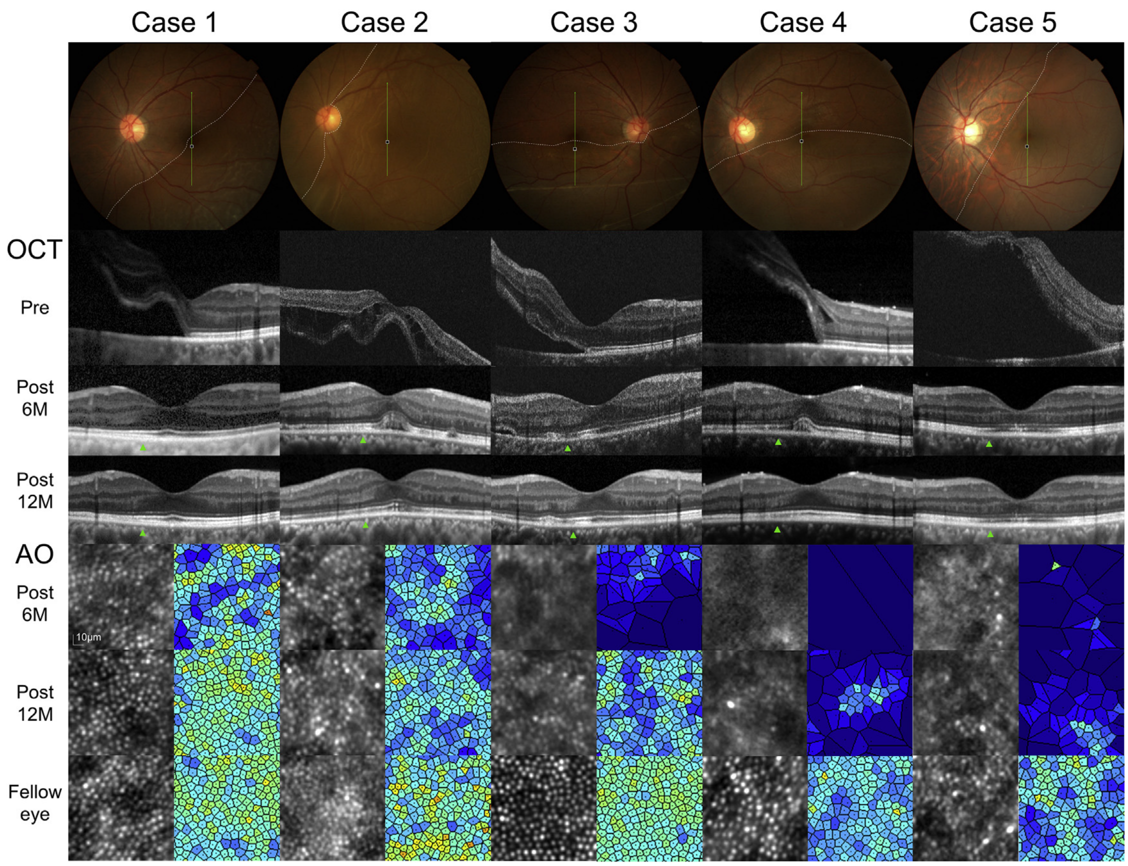

FIGURE 3. Representative images of 5 cases. Note the gradual recovery of the outer retina in the optical coherence tomography (OCT) images and the gradual increase in cone density in the adaptive optics (AO) images. The white and green lines in the fundus images indicate areas of retinal detachment and locations of OCT scans, respectively. The white small squares in the fundus images and the green small arrowheads in the OCT images indicate the locations of the measurements.

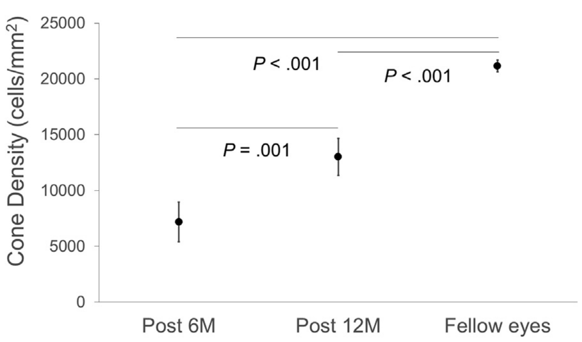

FIGURE 4. Changes in cone density in eyes with macula-off rhegmatogenous retinal detachment after surgery and in fellow eyes.

with cone density was IZ-RPE thickness at 6 months after surgery (standardized B = 0.775; B = 338.372; 95% CI, 164.698–512.047; $P = .001$) and at 12 months after surgery (standardized B = 0.639; B = 292.674; 95% CI, 123.465–461.883; $P = .002$) (Figure 5, Middle). Stepwise analysis also showed that the OCT factor most associated with the increase in cone density from 6 to 12 months after surgery was the increase in IZ-RPE thickness (standardized B = 0.794; B = 300.464; 95% CI, 155.619–445.309; $P = .001$) (Figure 5, Bottom).

• **REPRODUCIBILITY:** The intragrader ICC for cone density measurement was 0.93, while the intergrader ICC was 0.89. Thus, the reproducibility of the cone density measurements using AO detect software was confirmed.

DISCUSSION

NORMAL HUMAN VISION IS AFFECTED BY VARIOUS ABERRATIONS that degrade image quality. The history of AO began with the proposal by Babcock in 1953.[30] He proposed that AO in ground-based telescopes could correct the dynamic wavefront error caused by atmospheric turbulence, and this technique was successfully applied in the field of astronomy.[31] Thereafter, AO was applied to the imaging system

TABLE 2. Summary of Outer Layer Thickness (μm)

Parameter	Affected Eye		Fellow Eye (Group 3)	ANOVA *P* Value	Comparison Between Groups	Post Hoc *P* Value[a]
	Month 6 (Group 1)	Month 12 (Group 2)				
ONL thickness	89.4 ± 10.3	91.8 ± 11.3	95.8 ± 10.7	.17		
ELM-EZ thickness	27.9 ± 2.3	28.4 ± 3.7	29.2 ± 2.6	.36		
EZ-IZ thickness	23.3 ± 15.9	29.3 ± 12.1	28.9 ± 2.2	.18		
IZ-RPE thickness	21.0 ± 16.0	28.7 ± 12.3	33.6 ± 2.7	.004	1 vs 2	.045
					1 vs 3	.001
					2 vs 3	.408
EZ-RPE thickness	46.8 ± 22.0	57.6 ± 4.1	62.5 ± 2.7	.001	1 vs 2	.033
					1 vs 3	.001
					2 vs 3	.415
ELM-RPE thickness	83.6 ± 5.0	87.0 ± 4.3	90.0 ± 4.1	<.001	1 vs 2	.054
					1 vs 3	<.001
					2 vs 3	.082

ANOVA = analysis of variance; ELM = external limiting membrane; EZ = ellipsoid zone; IZ = interdigitation zone; ONL = outer nuclear layer; RPE = retinal pigment epithelium.

Data are presented as mean ± standard deviation.

[a]Post hoc comparison using the Tukey test.

TABLE 3. Comparison of Outer Layer Thickness Between Eyes With and Without Interdigitation Zone

Parameter	IZ (+)	IZ (−)	*P* Value[a]
Month 6			
Cone density, cells/mm^2	9600.1 ± 1962.3	555.0 ± 537.8	<.001
ONL thickness, μm	90.9 ± 10.3	83.8 ± 9.4	.23
ELM-EZ thickness, μm	28.1 ± 2.1	27.2 ± 3.0	.44
EZ-RPE thickness, μm	52.6 ± 15.3	35.3 ± 30.6	.15
ELM-RPE thickness, μm	84.1 ± 5.3	81.0 ± 1.7	.34
Month 12			
Cone density, cells/mm^2	15 944.3 ± 879.6	6374.7 ± 1770.8	<.001
ONL thickness, μm	93.5 ± 11.3	86.6 ± 10.7	.25
ELM-EZ thickness, μm	28.9 ± 3.9	27.0 ± 3.0	.29
EZ-RPE thickness, μm	58.7 ± 4.0	57.5 ± 3.3	.51
ELM-RPE thickness, μm	88.3 ± 4.1	83.7 ± 3.1	.02

ELM = external limiting membrane; EZ = ellipsoid zone; IZ = interdigitation zone; ONL = outer nuclear layer; RPE = retinal pigment epithelium.

Cone density is presented as mean ± standard error; optical coherence tomography data are presented as mean ± standard deviation.

[a]*P* value based on unpaired *t* test.

of the eyes. Liang and associates corrected ocular aberrations using an AO system with a Hartmann-Shack wavefront sensor and a deformable mirror.[31] With improvement in AO technology, the photoreceptor mosaic, fine structures of blood vessels, and nerve fibers were visualized.[32–36]

The present study showed a long-term increase in cone density after buckling surgery for rhegmatogenous retinal detachment. Cone density measured by the AO camera and IZ-RPE thickness measured by OCT images significantly recovered from 6 months to 12 months after surgery, but cone density at 12 months was still significantly lower than that in fellow eyes, whereas IZ-RPE thickness was not significantly different from that in fellow eyes. The study also showed that cone density was associated with IZ-RPE thickness and that the increase in cone density was associated with the increase in IZ-RPE thickness. There were no significant differences in ONL, ELM-EZ, and EZ-IZ thickness between affected and fellow eyes at 12 months after surgery.

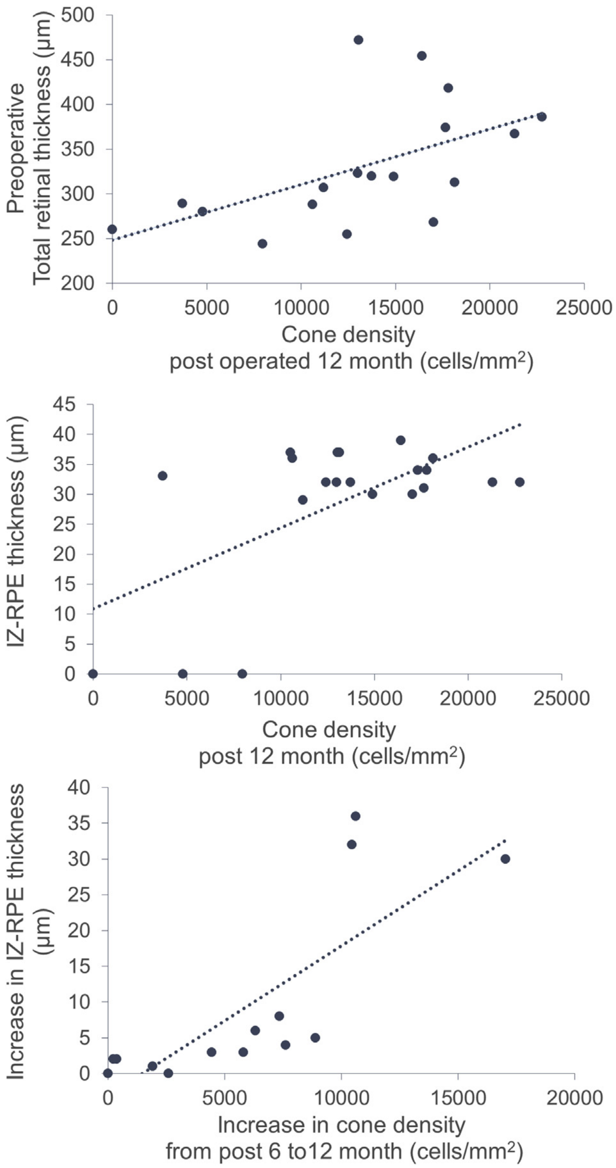

FIGURE 5. Scatter plots showing the association between cone density at 12 months and optical coherence tomography (OCT) parameters. (Top) Cone density after surgery was significantly associated with preoperative total retinal thickness. (Middle) Cone density after surgery was significantly associated with postoperative interdigitation zone (IZ) – retinal pigment epithelium (RPE) thickness. (Bottom) Increase in IZ-RPE thickness was significantly associated with increase in cone density after surgery.

The outer segments of the photoreceptors[35,37,38] or the IZ in OCT images[39] are reported to substantially contribute to the reflectance of the cone photoreceptor mosaic in AO images. There is a cone sheath between the IZ and the RPE.[40] Therefore, decrease in cone density and IZ-RPE thickness may suggest damage of the outer segments of the cone cells and cone sheath. Increase in cone density, IZ-RPE thickness, and EZ-RPE thickness may suggest regeneration of the outer segments and interdigitation between the outer segment and the cone sheath.

Retinal detachment occurs between the RPE and the photoreceptor outer segments. Photoreceptor outer segments are damaged after retinal detachment, and regenerate after the retina's reattachment. Therefore, IZ is a good marker for photoreceptor damage and regeneration in the OCT analysis. In eyes with more severe retinal damage, because EZ is also damaged, EZ can be a better marker than IZ. Because we performed surgery on the day of diagnosis or on the day after, retinal damage in this study may be mild and thus IZ was a better marker than EZ. The relatively good postoperative average BCVA (logMAR) at 12 months after surgery of 0.07 (= 20/23.5) appears to support this hypothesis.

Several studies have used OCT to evaluate recovery of the outer layers after surgery for rhegmatogenous retinal detachment. In these studies, the outer retina recovered after surgery with improvement in visual acuity.[7,41] In our study, EZ-RPE and IZ-RPE thicknesses were significantly less than those in fellow eyes at 6 months but were not significantly different from those in fellow eyes at 12 months. In contrast, cone density at 12 months was significantly decreased (63%) compared with that in fellow eyes. AO allows for direct visualization of this recovery process by showing cone cell images and may be able to detect smaller changes than those detected by OCT. Complete OCT recovery does not mean complete photoreceptor recovery, and AO may be a better examination than OCT. The axial resolution of Spectralis OCT is about 7 µm and its lateral resolution is 14 µm. In contrast, lateral resolution of the rtx1 AO fundus camera is only 2–4 µm. This difference in lateral resolution may affect the sensitivity to detect the regeneration of outer segments. The current gold-standard examination to evaluate retinal status is OCT. Despite the limitations of AO, such as the narrow field of view and insufficient ability to correct aberration in cases of media opacities, its ability to measure cone density is useful to evaluate retinal status and AO can be the additional gold-standard examination to evaluate retinal status in future.

Saleh and associates reported a decrease in cone density in eyes with rhegmatogenous retinal detachment 6 weeks after vitrectomy, and a high correlation of cone density with postoperative visual acuity and EZ-RPE thickness.[26] Because the surgical method and follow-up duration are different from those in our study, it is not possible to compare directly with this study. There may be differences between vitrectomy and scleral buckling in the regeneration of cone outer segments after surgery, because the disappearance of subretinal fluid is faster in vitrectomy than in scleral buckling. The outer retina of the macula was reported to be significantly thicker after buckling surgery than after vitrectomy.[42] Further studies are needed to evaluate the differences between the results of vitrectomy and scleral buckling surgery. Saleh and associates also reported a significant correlation between cone density and BCVA, whereas cone density was not significantly associated with BCVA at either 6 or 12 months after surgery in the current study. This is probably because the macula was not totally detached in 71% of the eyes and also because of the small sample size. Local sensitivity measurement using fundus microperimetry may be able to show the correlation between the local visual function and cone density.[43,44] Further study is needed to evaluate the relationship between visual function and cone density.

There have been several experimental studies of retinal detachment.[45–47] Guerin and associates described the recovery process after retinal detachment.[46] During 7 days of retinal detachment, the inner segment remained intact. In our study, the thickness of the inner segment (ie, ELM-EZ) was not significantly different in eyes with retinal detachment and fellow eyes. This is probably owing to the short time between the onset of detachment and surgery in this case series. Guerin and associates also reported a positive correlation between outer segment length and duration of reattachment. This recovery process may be the same as the increase in cone density measured by AO and the increase in outer layer thickness measured by OCT. In addition, although Guerin and associates observed the recovery process for up to 150 days, our study and another study[41] showed that this process may continue for at least 12 months. Because there are patients who continue to experience improvement in vision beyond 12 months after buckling surgery, further study is needed to assess the duration of the regeneration process.

There are several limitations to this study. First, we could not obtain cone packing images at the fovea, because the resolution of the AO fundus camera is not sufficient to permit visualization of cone cells in the fovea. Therefore, we measured cone density at 2 degrees from the fovea, where cone density is much less than in the fovea but most of the cells are cones.[48] Second, we could not evaluate changes in cone density in the early postoperative period, because postsurgical effects, such as inflammation, irregular refractive changes, and media opacities, prevented us from obtaining cone packing images at earlier times. Third, cone images are sometimes not clear in the AO fundus camera. A new technique called split detector using AO-SLO has been developed.[35,49] The images of cone packing obtained by the split detector system are much clearer than those obtained by the AO fundus camera, although the cell images in the split detector system are the inner segments of the cone cells whereas the cell images in the AO fundus camera are the outer segments of the cone cells. Simultaneous usage of split detector may help to improve understanding of the cone cell recovery process after reattachment. Fourth, detached retina makes an acute angle with the attached retina in some eyes, and identification of the location of the retina 2 degrees from the fovea may not be accurate in such cases. Fifth, because of the retrospective study design, the results may have been affected by selection bias.

In conclusion, reattached retinas were examined by AO and OCT in eyes with fovea-off rhegmatogenous retinal detachment. Cone density increased from 6 months to 12 months after surgery but was still lower than that in normal fellow eyes. IZ-RPE, EZ-RPE, and ELM-RPE thicknesses increased from 6 to 12 months, and these measurements were not different from those in normal fellow eyes. Cone density at 12 months was significantly associated with IZ-RPE, and increased cone packing density was significantly associated with increased IZ-RPE. The recovery of cone packing density observed by AO was associated with structural recovery of the outer retina observed by OCT.

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