Association between photoreceptor regeneration and visual acuity following surgery for rhegmatogenous retinal detachment

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ABSTRACT

Purpose: To evaluate foveal regeneration and the association between retinal restoration and visual acuity following reattachment of rhegmatogenous retinal detachment (RRD).

Methods: Twenty-nine eyes of 29 patients with successfully reattached macula-off RRD were retrospectively analyzed. We used Spectral-domain optical coherence tomography to image macular regions and measure retinal thickness and Snellen VA chart to evaluate best-corrected visual acuity (BCVA) at 1, 2, 3, 6, 9, and 12 months after vitrectomy. The data of BCVA were converted to the logarithm of the minimum angle of resolution scale. Opposite eyes were used as controls.

Results: The thicknesses of the external limiting membrane (ELM)-ellipsoid zone (EZ) and EZ-retinal pigment epithelium (RPE) were significantly thinner in involved eyes than in corresponding unaffected eyes at 1 month after surgery ($P < 0.001$ for both), with the thickness increasing over time ($P < 0.001$ for both). BCVA significantly improved over time ($P < 0.001$) and the improvement correlated with EZ-RPE thickness ($r = -0.45$, $P = 0.021$). Multiple regression analysis demonstrated the presence of a foveal bulge as an independent predictor of final BCVA ($P < 0.001$). Eyes with a foveal bulge had significantly better BCVA and greater EZ-RPE thickness than those without throughout the follow-up period. Significant restoration of the integrity of EZ and cone interdigitation zone (CIZ) was observed over time ($P < 0.001$ for both) in eyes with a foveal bulge.

Conclusions: The thickness of EZ-RPE and cone density increased during foveal regeneration, as demonstrated by the continuous improvements in CIZ integrity over time, leading to the formation of the foveal bulge and good vision following

successful reattachment of macula-off RRD.

Introduction

Rhegmatogenous retinal detachment (RRD) is a sight-threatening pathology. Currently, the only treatment modality for RRD is retinal reattachment.[1] Although the anatomical success rate of retinal reattachment is high,[2-4] patients are often disappointed with improvements in best-corrected visual acuity (BCVA) following surgery, particularly in eyes affected by macular detachment. Photoreceptor volume has been shown to be reduced in cases of macula-off RRD (ie, separation of the macula from the retinal pigment epithelium [RPE]) compared to cases of macula-on RRD.[5] Persistent functional damage to the macula is observed in a proportion of eyes affected by macula-off RRD.[6-11] Factors reportedly associated with functional recovery following macula-off RRD include preoperative VA,[12] duration of macular detachment,[6,8] height of macular detachment,[13,14] and age.[12] Even among eyes predicted to have good postoperative vision due to good preoperative condition and the absence of significant complications during surgery, some eyes continue to have poor visual acuity.

Technological advantages in spectral-domain optical coherence tomography (SD-OCT) have allowed detailed retinal evaluation and understanding of the foveal microstructure recovery process after RRD. The Spectralis (Heidelberg Engineering, Heidelberg, Germany), which incorporates software with an eye-movement tracking function, can perform serial scans at the same location, thus allowing the precise evaluation of changes occurring at given retinal areas.[15] Many studies using SD-OCT have demonstrated that integrity of the ellipsoid zone (EZ; ie, the junction between the inner and outer segment of photoreceptors) and external limiting membrane (ELM) is significantly correlated with BCVA following retinal reattachment.[5,16-21] However, these reports had considerable limitations, including inconsistencies between the duration and location of images taken, a lack of objective assessment of membrane integrity, and decreased band reflectivity due to fragmentation or thinning, which can be observed in 5% of healthy eyes as a result of artifact.[22]

Careful examination of the SD-OCT images of normal eyes demonstrated bulging of the EZ at the central fovea, termed a foveal bulge. Recent OCT studies have shown that the presence or absence of a foveal bulge at the central fovea is significantly correlated with visual acuity in eyes with albinism,[23] occult macular dystrophy,[24] amblyopia[25] and branch retinal vein occlusion[26]. Hasegawa *et al.* reported a significant correlation between the presence of a foveal bulge and BCVA after successful RRD repair with vitrectomy.[27] The authors supported the utility of evaluating foveal bulge and foveal photoreceptor outer segment (OS) length in determining the visual properties of eyes successfully treated with retinal reattachment.[27] However, this study did not evaluate retinal layer thickness over time, including OS length, or the time required for foveal bulge regeneration following successful retinal reattachment.

There is a lack of data regarding changes in retinal layer thickness and the correlation between thickness changes and BCVA outcomes following successful RRD repair. Dell'Omo *et al.*[28] and Terauchi *et al.*[29] performed serial evaluations of changes in retinal layer thickness at the same location with SD-OCT and observed progressive increases in the thickness of several central retinal layers. However, assessments of the relationship between retinal layer thickness and vision were limited in these studies. The direct correlation between increased retinal layer thickness and improvements in BCVA was unclear as parameters were not directly compared over time. In addition, no significant relationship between foveal bulge regeneration and visual acuity was observed.

Thus, the goal of the present study was to quantify changes in retinal layer thickness and evaluate its relationship to improvements in BCVA, and to investigate the time required for regeneration of the foveal bulge following successful retinal reattachment and any potential association with postoperative BCVA.

Methods

Ethics statement

This retrospective, observational, comparative, single-center study followed the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board and Ethics Committee of the Nagoya University Graduate School of Medicine.

Measurement using optical coherence tomographic images

A Spectralis SD-OCT was used to obtain all SD-OCT images. We evaluated horizontal cross-section images recorded at each visit after successful retinal reattachment. Retinal layer thickness was measured on the same selected central foveal scan throughout follow-up using the computer-based caliper measurement tool of the SD-OCT system. Central foveal thickness (CFT) was measured as the thickness between the surface of the internal limiting membrane (ILM) and the outer border of RPE at the central fovea (Figure 1). The thickness of the outer nuclear layer (ONL) was defined as the distance between the outer borders of ILM and ELM. The ELM-EZ thickness (inner segment (IS) thickness) was defined as the distance between the outer borders of ELM and EZ.[30] The EZ-RPE thickness (OS thickness) was defined as the distance between the outer border of EZ and the inner border of RPE.

Retinal layer thickness was measured manually at the foveal bulge (if visible) by operators masked to VA values and other information including the pre-operative status. A foveal bulge was defined as an EZ-RPE thickness at the central fovea >10 μm greater than the average EZ-RPE thickness at 250 μm temporal and nasal to the central fovea. In cases where the foveal bulge was not visible, measurements were performed along a vertical line passing through the steepest part of the foveal excavation. Identical measurements were performed in opposite eyes as controls.

The integrity of the foveal ELM, EZ, and cone interdigitation zone (CIZ) was evaluated for in a 1-mm-diameter area for each image on a 4-point scale as follows: 1, line not visible; 2, line disruption >200 μm; 3, line disruption <200 μm; and 4, continuous line. Identical measurements were performed in opposite eyes as controls.

Subjects

We retrospectively reviewed all patients who had undergone successful RRD repair with vitrectomy at the Nagoya University Hospital from June 2012 to May 2014 in whom the EZ line at the central fovea could be observed in follow-up SD-OCT images. All patients signed an informed consent form prior to surgery.

Patients were initially classified into two groups according to preoperative macula status, evaluated using preoperative SD-OCT macular scans: macula-off RRD (retinal detachment involving the macula) and macula-on RRD (retinal detachment not involving the macula). Patients were further classified into two subgroups according to the presence of a foveal bulge, which was evaluated at each follow-up visit.

All patients underwent a comprehensive ophthalmic examination, including measurements of BCVA, IOP, and axial length; slit-lamp examination; fundus examination; and SD-OCT before and at 1, 3, 6, 9, and 12 months after surgery. Snellen VA values were converted to the logarithm of the minimum angle of resolution (LogMAR) units in order to create a linear scale of VA.

Surgical technique

Standard 3-port pars plana vitrectomy was performed with 25-gauge instruments after retrobulbar anesthesia with 2.5 ml each of 2% lidocaine and 0.5% bupivacaine. No patients underwent concurrent scleral buckling surgery. In eyes with a cataract, cataract surgery was performed as described below. A 2.4-mm-wide self-sealing superior sclerocorneal tunnel was created at the 12 o'clock position, and a continuous curvilinear capsulorhexis was performed. The lens nucleus was removed, and the residual cortex was aspirated with an irrigation/aspiration (I/A) tip. Next, a foldable acrylic intraocular lens was implanted into the bag. A trocar was then inserted at approximately 30° parallel to the limbus with the bevel-side up. Once the trocar was past the trocar sleeve, the angle was changed to perpendicular to the surface. After creating 3 ports, vitrectomy was performed using the Constellation® system (Alcon Laboratories, Inc., Fort Worth, TX). After fluid-air exchange and subretinal fluid drainage from the causative retinal tear(s) or iatrogenic hole were performed, intraoperative photocoagulation was applied to the causative retinal tear(s) or iatrogenic hole (if present). At completion of vitrectomy, 20% sulfur hexafluoride (SF_6) was injected into the vitreous. After IOP was adjusted to a normal tension, cannulae were withdrawn, and the sclera was pressed and massaged with an indenter to close the wound.

Exclusion criteria

Exclusion criteria included dense ocular media (eg, vitreous hemorrhage, vitreous opacity), preexisting macular conditions (eg, macular degeneration, vascular occlusive diseases, or diabetic retinopathy), proliferative vitreoretinopathy (PVR) ≥grade C,[31] and clinically evident postoperative change likely to interfere with accurate evaluation of retinal layers (eg, recurrent RRD, epiretinal membrane, cystoid macular edema, or persistent subretinal fluid).

Statistical analysis

The values are presented as the mean ± standard deviation. Independent t-test was used to compare normally distributed data and the Chi-square test for categorical data. One way analysis of variance (ANOVA) was used to evaluate changes in BCVA, retinal layers thickness, and the integrity of outer retinal bands over time. After a linear approximate equation was employed for calculating the slopes of BCVA and EZ-RPE/ELM-EZ thickness for each eye (supplement figure), Pearson's correlation coefficient test was used to evaluate the association between them. Multiple linear regression analysis was used to evaluate the association between final BCVA and independent variables, including the presence of foveal bulge, EZ-RPE thickness, preoperative BCVA, age, axial length, and duration of retinal detachment. $P < 0.05$ was considered statistically significant.

Results

Patient demographics and surgical parameters

Between June 2012 and May 2014, 53 eyes of 53 patients with macula-off RRD and 26 eyes of 26 patients with macula-on RRD underwent vitrectomy at our department for the repair of RRD. Of these, 37 eyes were excluded for the following reasons: presence of PVR grade C or worse (n = 3), vitreous hemorrhage (n = 1), macular hole (n = 1), diabetic retinopathy (n = 1), postoperative development of dense cataract (n = 2), macular edema (n = 2), subretinal fluid (n = 6), or significant epiretinal membrane (n = 1) at any time of follow-up, or an incapacity to attend regular follow-up visits (n = 20). As a result, 29 eyes with macula-off RRD and 13 eyes with macula-on RRD were included in final analysis. Patient demographics and surgical parameters are shown in Table 1. No significant intergroup differences in age, sex, axial length, or surgical procedures were observed, except for preoperative BCVA (logMAR; $P < 0.001$).

Changes of retinal thickness and BCVA over time following surgery for macula-off and macula-on RRD

In eyes affected by macula-on RRD, no significant differences in BCVA or thicknesses of CFT, ONL, ELM-EZ, or EZ-RPE were observed during the follow-up period, with no significant differences in any parameter observed compared to control eyes (Figure 2, Table 2).

Significantly increased thickness was observed at the level of ELM-EZ (IS thickness, 25.2 ± 4.8 to 31.4 ± 2.6 μm; $P < 0.001$; Figure 3A; Table 2) and EZ-RPE (OS thickness, 25.4 ± 10.4 to 41.1 ± 5.6 μm; $P < 0.001$) between postoperative months 1 and 12 (Figure 3B) in the macula-off RRD group, with no significant difference observed in CFT or ONL thickness over time (Figure 3C, 3D). The mean

EZ-RPE thickness was significantly thinner in eyes affected by macula-off RRD compared to control eyes throughout the follow-up period (Figure 3B; **P < 0.001). The mean ELM-EZ thickness was significantly thinner in eyes affected by macula-off RRD compared to control eyes until 6 months postoperatively (Figure 3A; **P < 0.001, *P < 0.01).

In eyes affected by macula-off RRD, the mean postoperative BCVA significantly improved from 0.39 ± 0.29 to 0.15 ± 0.14 between postoperative months 1 and 12 (P < 0.001; Figure 4A; Table 2), but remained worse than control eyes at 12 months.

The slope of the regression line for change in BCVA over time (see supplement file) was significantly correlated with EZ-RPE thickness over time (r = −0.45; P = 0.021; Figure 4B) but not with ELM-EZ thickness (r = −0.16; P = 0.422; Figure 4C).

Multiple stepwise regression analysis for final BCVA (Table 3) revealed only the presence of a foveal bulge as an independent predictor of final VA (P < 0.001).

Differences between eyes with and without a foveal bulge in the macula-off RRD group

Clinical characteristics of the macula-off RRD group with or without the presence of a foveal bulge are shown in Table 4. A foveal bulge was observed in 17 eyes (Figure 5) and not in 12 (Figure 6) during the follow-up period. No significant differences in any clinical characteristic, including age, sex, duration of macular detachment, preoperative BCVA, and axial length, were observed between patients with and without the presence of a foveal bulge.

The mean postoperative BCVA in eyes with a foveal bulge was significantly better than in eyes without a foveal bulge throughout the follow-up period. (P <

0.001; Table 5). Mean postoperative BCVA significantly improved from 0.23 ± 0.14 to 0.05 ± 0.07 between postoperative months 1 and 12 in eyes with a foveal bulge (P = 0.035), but not in eyes without a foveal bulge (Table 5). In addition, EZ-RPE thickness was significantly greater in eyes with a foveal bulge than in eyes without a foveal bulge throughout the follow-up period (P < 0.001; Table 5). Further, EZ-RPE thickness significantly increased from 28.0 ± 8.6 to 46.3 ± 5.9 μm between postoperative months 1 and 12 in eyes with a foveal bulge (P < 0.001), but no significant improvement was observed in eyes without a foveal bulge.

The time at which a foveal bulge was first observed varied between 1 and 12 months postoperatively and was not associated with final BCVA (r = 0.27; P = 0.281; Figure 7).

During the follow-up period, significant restoration of the integrity of EZ and CIZ was observed in eyes with a foveal bulge (both P < 0.001) and of EZ in eyes without a foveal bulge (P < 0.001; Table 5). The integrity of CIZ significantly differed between these two groups throughout the follow-up period (P < 0.001 to P < 0.05 at different time points).

Discussion

Our results showed that ELM-EZ thickness (IS thickness) and EZ-RPE thickness (OS thickness) were thinned in eyes affected by macula-off RRD compared to opposite unaffected eyes at 1 month after successful attachment, and then the thicknesses significantly increased over time, with partial restoration of the integrity of the outer retinal bands. In eyes affected by macula-off RRD, BCVA significantly improved between postoperative months 1 and 12. In addition, the slope of the regression line for change in EZ-RPE thickness over time significantly correlated with that of BCVA over time. Foveal bulge was an independent predictor of final BCVA. Eyes with a foveal bulge had significantly better BCVA and greater EZ-RPE thickness than those without a foveal bulge throughout the follow-up period.

SD-OCT provides direct visualization of *in vivo* retinal morphology, allowing the individual layers of the macula to be observed at high resolution, thereby providing greater information on structural postoperative macular changes. Recent OCT studies have reported disruptions of photoreceptor microstructures and integrity of the outer retinal bands at the fovea in cases of macula-off RRD[5,17-19,32,33] as well as several other retinal diseases (eg, macular hole[20,34] and central serous chorioretinopathy[35]). In the present study, SD-OCT allowed the precise measurement of retinal layer thickness and the evaluation of outer retinal band integrity. Regarding thinning of the retinal layer following RRD, experimental studies have demonstrated dropout of OS photoreceptors due to RD-induced separation of the OS from the RPE, thereby disrupting normal OS renewal and leading to OS shortening and eventual degeneration.[36-39] Detachment of the neural retina from the RPE induces a variety of changes in several cell types (eg, photoreceptors, RPE, Muller cell, and so on) throughout the retina.[10]

There has been a more limited time-sequenced data regarding the time course of retinal layer thickness changes and the association with BCVA outcomes following successful macula-off RRD repair. Two recent studies reported the thickness of retinal layers to be significantly thinned after successful attachment and gradually increases, with only EZ-RPE thickness remaining thinner than the opposite unaffected eye at 12 months postoperatively.[28,29] Our results corroborate these findings.

In addition to changes in retinal layer thickness following successful retinal reattachment, BCVA in eyes with macula-off RRD significantly improved between postoperative months 1 and 12 in the present study. Previous studies[28,29] evaluated the relationship between improvements in BCVA and the thickness of EZ-RPE or ELM-EZ at particular time points postoperatively, eg, 1 month or 12 months; however, increased retinal layer thickness and improvements in BCVA were not directly compared over time. Accordingly, the association between improvements in BCVA and increased retinal layer thickness remains unclear. We calculated a linear approximate equation for the association between BCVA and ELM-EZ or EZ-RPE thickness over time, and observed a significant correlation between the slopes of the regression lines for change in EZ-RPE thickness and BCVA over time. We found that BCVA improved in parallel with increased EZ-RPE thickness (OS thickness) following successful retinal reattachment.

Factors previously reported to be associated with functional recovery after macula-off RRD include preoperative VA,[12] duration of macular detachment,[6,8] height of macular detachment,[13,14] and age.[12] In the present study, the presence of a foveal bulge was the only significant independent predictor of final BCVA. Perhaps the number of patients we included was insufficient to evaluate the aforementioned factors. Recent OCT studies have demonstrated the presence or absence of a foveal bulge at the central fovea is significantly associated with visual acuity in eyes with albinism,[23] occult macular dystrophy,[24] amblyopia,[25] branch retinal vein occlusion,[26] and RRD.[27] Centripetal migration of cone cells and thinning of individual foveal cone OS reportedly results in an increase in foveal cone OS density.[40] Hasegawa *et al.* suggested that increased foveal photoreceptor OS length was related to the presence of a foveal bulge on OCT imaging, indicating high foveal cone OS density in eyes with a foveal bulge.[26,27] We found that BCVA was significantly better in eyes with a foveal bulge than those without throughout the follow-up period. Our results indicate the presence of a foveal bulge is essential for achieving good final vision, and corroborate the previous findings of an association between formation of a foveal bulge and vision. On the other hand, no association was observed between final BCVA and time until the first appearance of a foveal bulge after surgery. This result indicates that eyes with a foveal bulge are more likely to have better final vision regardless of the time required for the reappearance of a foveal bulge after macula-off RRD.

In eyes that eventually developed a foveal bulge, BCVA was significantly greater even at 1 month postoperatively when no eyes were seen to have a foveal bulge. In addition, EZ-RPE thickness and the integrity of EZ and CIZ significantly differed between eyes with and without foveal a bulge from 1 month postoperatively. These results indicate regeneration of the foveal structure after macula-off RRD occurs earlier in eyes with a foveal bulge, resulting in better BCVA even before the formation of a foveal bulge. Perhaps eyes with a foveal bulge have less macular damage prior to surgery or increased photoreceptor regeneration in eyes with macula-off RRD. These findings indicate EZ-RPE thickness or integrity of outer bands during the early postoperative period may be good predictors of the formation of a foveal bulge during the follow-up period and the achievement of a good final BCVA.

Cone photoreceptor density is an important consequence for achieving good BCVA. Ooto *et al.* used an adaptive optics scanning laser ophthalmoscope to determine cone photoreceptor density and compared their findings with microstructures determined by a commercially available SD-OCT.[41] They found the mean cone density in eyes with a disrupted CIZ line was significantly lower than that in eyes with an intact CIZ line, and cone density in the foveal area was correlated with BCVA. Of the outer retinal bands, the integrity of CIZ was better in eyes with a foveal bulge throughout the follow-up period in the present study, corroborating the findings of Ooto *et al.* as the presence of a foveal bulge on OCT imaging has previously been shown to indicate high foveal cone OS density.[26,27] Taken together, these findings indicate EZ-RPE thickness (the OS thickness) and cone density increase during foveal regeneration, observed as a continuous CIZ line, would be associated with the formation of a foveal bulge and better final vision in eyes following successful reattachment of macula-off RRD.

There are limitations to the present study. This was a retrospective study with a relatively small sample size, which may have resulted in an insufficient number of participants for adequate comparison of preoperative BCVA and other factors, such as age and duration of macular detachment. Another limitation is the follow-up period of 12 months. As EZ-RPE thickness may increase after 12 months postoperatively, further longitudinal studies are required to confirm complete recovery of EZ-RPE thickness to the same level as that of the corresponding healthy eye. Further, we did not evaluate the preoperative microstructure of retinal layers using SD-OCT imaging. Although no significant differences in preoperative BCVA were observed between eyes with and without a foveal bulge, retinal microstructure may have differed between these groups prior to surgery, particularly as restoration of the integrity of the outer retinal bands differed between these groups even during the early postoperative period. In addition, retinal layer distances were manually measured as automated calculation of retinal layer thicknesses may be technically challenging in eyes with fragmented or poorly visualized retinal layers. Further prospective studies with larger sample sizes and automated calculation of retinal thicknesses and assessments of outer retinal bands are required.

In conclusion, the findings of the present study demonstrate ELM-EZ (IS thickness) and EZ-RPE thickness (OS thickness) in eyes with a reattached RRD are significantly thinner immediately after surgery, and progressive recovery of thickness and restoration of the outer retinal layers/bands at the fovea occurs following macula-off RRD repair. During foveal regeneration, increased EZ-RPE thickness (OS thickness) and cone density, observed as a continuous CIZ, would be associated with the formation of a foveal bulge and better final vision in eyes following successful reattachment of macula-off RRD.

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References

1. D'Amico DJ. Clinical practice. Primary retinal detachment. N Engl J Med. 2008;359:2346-2354.
2. Goto T, Nakagomi T, Iijima H. A comparison of the anatomic successes of primary vitrectomy for rhegmatogenous retinal detachment with superior and inferior breaks. Acta Ophthalmol. 2013;91:552-556.
3. Campo RV, Sipperley JO, Sneed SR, et al. Pars plana vitrectomy without scleral buckle for pseudophakic retinal detachments. Ophthalmology. 1999;106:1811-1815; discussion 1816.
4. Tan HS, Oberstein SY, Mura M, Bijl HM. Air versus gas tamponade in retinal detachment surgery. Br J Ophthalmol. 2013;97:80-82.
5. Gharbiya M, Grandinetti F, Scavella V, et al. Correlation between spectral-domain optical coherence tomography findings and visual outcome after primary rhegmatogenous retinal detachment repair. Retina. 2012;32:43-53.
6. Diederen RM, La Heij EC, Kessels AG, Goezinne F, Liem AT, Hendrikse F. Scleral buckling surgery after macula-off retinal detachment: worse visual outcome after more than 6 days. Ophthalmology. 2007;114:705-709.
7. Ross WH, Kozy DW. Visual recovery in macula-off rhegmatogenous retinal detachments. Ophthalmology. 1998;105:2149-2153.
8. Hassan TS, Sarrafizadeh R, Ruby AJ, Garretson BR, Kuczynski B, Williams GA. The effect of duration of macular detachment on results after the scleral buckle repair of primary, macula-off retinal detachments. Ophthalmology. 2002;109:146-152.
9. Ozgur S, Esgin H. Macular function of successfully repaired macula-off retinal detachments. Retina. 2007;27:358-364.

10. Erickson PA, Fisher SK, Anderson DH, Stern WH, Borgula GA.. Retinal detachment in the cat: the outer nuclear and outer plexiform layers. Invest Ophthalmol Vis Sci. 1983;24:927-942.

11. Mitry D, Awan MA, Borooah S, et al. Long-term visual acuity and the duration of macular detachment: findings from a prospective population-based study. Br J Ophthalmol. 2013;97:149-152.

12. Tani P, Robertson DM, Langworthy A. Prognosis for central vision and anatomic reattachment in rhegmatogenous retinal detachment with macula detached. Am J Ophthalmol. 1981;92:611-620.

13. Ross W, Lavina A, Russell M, Maberley D. The correlation between height of macular detachment and visual outcome in macula-off retinal detachments of < or = 7 days' duration. Ophthalmology. 2005;112:1213-1217.

14. Mowatt L, Tarin S, Nair RG, Menon J, Price NJ. Correlation of visual recovery with macular height in macula-off retinal detachments. Eye. 2010;24:323-327.

15. Grover S, Murthy RK, Brar VS, Chalam KV. Comparison of retinal thickness in normal eyes using Stratus and Spectralis optical coherence tomography. Invest Ophthalmol Vis Sci. 2010;51:2644-2647.

16. Smith AJ, Telander DG, Zawadzki RJ, et al. High-resolution Fourier-domain optical coherence tomography and microperimetric findings after macula-off retinal detachment repair. Ophthalmology. 2008;115:1923-1929.

17. Schocket LS, Witkin AJ, Fujimoto JG, et al. Ultrahigh-resolution optical coherence tomography in patients with decreased visual acuity after retinal detachment repair. Ophthalmology. 2006;113:666-672.

18. Wakabayashi T, Oshima Y, Fujimoto H, et al. Foveal microstructure and

visual acuity after retinal detachment repair: imaging analysis by Fourier-domain optical coherence tomography. Ophthalmology. 2009;116:519-528.

19. Shimoda Y, Sano M, Hashimoto H, Yokota Y, Kishi S. Restoration of photoreceptor outer segment after vitrectomy for retinal detachment. Am J Ophthalmol. 2010;149:284-290.

20. Itoh Y, Inoue M, Rii T, Hiraoka T, Hirakata A. Significant correlation between visual acuity and recovery of foveal cone microstructures after macular hole surgery. Am J Ophthalmol. 2012;153:111-119 e111.

21. Srinivasan VJ, Monson BK, Wojtkowski M, et al. Characterization of outer retinal morphology with high-speed, ultrahigh-resolution optical coherence tomography. Invest Ophthalmol Vis Sci. 2008;49:1571-1579.

22. Rii T, Itoh Y, Inoue M, Hirakata A. Foveal cone outer segment tips line and disruption artifacts in spectral-domain optical coherence tomographic images of normal eyes. Am J Ophthalmol. 2012;153:524-529 e521.

23. Thomas MG, Kumar A, Mohammad S, et al. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? Ophthalmology. 2011;118:1653-1660.

24. Chen CJ, Scholl HP, Birch DG, Iwata T, Miller NR, Goldberg MF. Characterizing the phenotype and genotype of a family with occult macular dystrophy. Arch Ophthalmol. 2012;130:1554-1559.

25. Al-Haddad CE, El Mollayess GM, Mahfoud ZR, Jaafar DF, Bashshur ZF. Macular ultrastructural features in amblyopia using high-definition optical coherence tomography. Br J Ophthalmol. 2013;97:318-322.

26. Hasegawa T, Ueda T, Okamoto M, Ogata N. Presence of foveal bulge in optical coherence tomographic images in eyes with macular edema associated with

branch retinal vein occlusion. Am J Ophthalmol. 2014;157:390-396 e391.

27. Hasegawa T, Ueda T, Okamoto M, Ogata N. Relationship between presence of foveal bulge in optical coherence tomographic images and visual acuity after rhegmatogenous retinal detachment repair. Retina 2014;34:1848-1853.

28. dell'Omo R, Viggiano D, Giorgio D, et al. Restoration of foveal thickness and architecture after macula-off retinal detachment repair. Invest Ophthalmol Vis Sci. 2015;56:1040-1050.

29. Terauchi G, Shinoda K, Matsumoto CS, Watanabe E, Matsumoto H, Mizota A. Recovery of photoreceptor inner and outer segment layer thickness after reattachment of rhegmatogenous retinal detachment. Br J Ophthalmol. 2015;99:1323-1327.

30. Staurenghi G, Sadda S, Chakravarthy U, Spaide RF. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN*OCT consensus. Ophthalmology. 2014;121:1572-1578.

31. Machemer R, Aaberg TM, Freeman HM, Irvine AR, Lean JS, Michels RM. An updated classification of retinal detachment with proliferative vitreoretinopathy. Am J Ophthalmol. 1991;112:159-165.

32. Nakanishi H, Hangai M, Unoki N, et al. Spectral-domain optical coherence tomography imaging of the detached macula in rhegmatogenous retinal detachment. Retina. 2009;29:232-242.

33. Lai WW, Leung GY, Chan CW, Yeung IY, Wong D. Simultaneous spectral domain OCT and fundus autofluorescence imaging of the macula and microperimetric correspondence after successful repair of rhegmatogenous retinal detachment. Br J Ophthalmol. 2010;94:311-318.

34. Itoh Y, Inoue M, Rii T, Hiraoka T, Hirakata A. Correlation between length of

foveal cone outer segment tips line defect and visual acuity after macular hole closure. Ophthalmology. 2012;119:1438-1446.

35. Matsumoto H, Kishi S, Otani T, Sato T. Elongation of photoreceptor outer segment in central serous chorioretinopathy. Am J Ophthalmol. 2008;145:162-168.

36. Sakai T, Calderone JB, Lewis GP, Linberg KA, Fisher SK, Jacobs GH. Cone photoreceptor recovery after experimental detachment and reattachment: an immunocytochemical, morphological, and electrophysiological study. Invest Ophthalmol Vis Sci. 2003;44:416-425.

37. Jackson TL, Hillenkamp J, Williamson TH, Clarke KW, Almubarak AI, Marshall J. An experimental model of rhegmatogenous retinal detachment: surgical results and glial cell response. Invest Ophthalmol Vis Sci. 2003;44:4026-4034.

38. Guerin CJ, Lewis GP, Fisher SK, Anderson DH. Recovery of photoreceptor outer segment length and analysis of membrane assembly rates in regenerating primate photoreceptor outer segments. Invest Ophthalmol Vis Sci. 1993;34:175-183.

39. Lewis GP, Charteris DG, Sethi CS, Leitner WP, Linberg KA, Fisher SK. The ability of rapid retinal reattachment to stop or reverse the cellular and molecular events initiated by detachment. Invest Ophthalmol Vis Sci. 2002;43:2412-2420.

40. Hendrickson A, Possin D, Vajzovic L, Toth CA. Histologic development of the human fovea from midgestation to maturity. Am J Ophthalmol. 2012;154:767-778 e762.

41. Ooto S, Hangai M, Sakamoto A, et al. High-resolution imaging of resolved central serous chorioretinopathy using adaptive optics scanning laser ophthalmoscopy. Ophthalmology. 2010;117:1800-1809, 1809 e1801-1802.

Figure Legends

Figure 1. Representative spectral-domain optical coherence tomographic (SD-OCT) image of a normal eye. A horizontal scan through the central fovea was obtained. Retinal zones were visualized by SD-OCT. Central foveal thickness (CFT) was defined as the distance between the surface of the internal limiting membrane (ILM) and the outer border of the retinal pigment epithelium (RPE) at the central fovea. Outer nuclear layer (ONL) thickness was measured as the distance between the outer border of the ILM and the outer border of the external limiting membrane (ELM) band. ELM–EZ thickness was measured as the distance between the outer border of the ELM band and the outer border of the ellipsoid zone (EZ). EZ–RPE thickness was measured as the distance between the outer border of EZ and the inner border of RPE. The SD-OCT image shown demonstrates bulging of ELM, EZ, and cone interdigitation zone (CIZ) at the central fovea, known as a foveal bulge.

Figure 2. A representative SD-OCT image of an eye with macula-on RRD before surgery (A). Thickness and reflectivity of the lines in the corresponding unaffected eye were similar to those of the affected eye prior to surgery (B). The ELM, EZ, and CIZ were visible without any disruption during the follow-up period and the foveal bulge was present during the follow-up period in eye affected by macula-on RRD (C).

Figure 3. Changes in mean retinal layers thickness in eyes with macula-off RRD after surgery and corresponding control eyes. Mean ELM-EZ thickness gradually increased in eyes with macula-off RRD over the postoperative period (A). ELM-EZ thickness was significantly thinner in eyes with macula-off RRD compared to control eyes until 6 months postoperatively. Mean EZ-RPE thickness gradually increased in eyes with macula-off RRD over time (B). EZ-RPE thickness was significantly thinner

in eyes with macula-off RRD compared to control eyes throughout the follow-up period. Mean CFT in eyes with macula-off RRD was significant thinner in control eyes at 1 month after surgery. No significant difference in ONL thickness was observed any time throughout the follow-up period. *P < 0.01; **P < 0.001.

Figure 4. Change in mean best-corrected visual acuity (BCVA) after vitreous surgery for macula-off RRD (A). The slope of the regression line from logMAR over time correlated with the slope of the EZ-RPE thickness over time ($r = -0.45$, P = 0.021; panel B), but not the slope of the regression line for ELM-EZ thickness over time ($r = -0.16$, P = 0.422; panel C). *P < 0.01; **P < 0.001; logMAR, logarithm of the minimum angle of resolution.

Figure 5. Representative SD-OCT images in an eye with thickening of the central fovea and reconstitution of the foveal bulge after repair of macula-off RRD. SD-OCT image demonstrating the preoperative status of the macula prior to surgery, with a visual acuity of 20/60 (A). The thickness and reflectivity of the outer bands were normal in the corresponding unaffected eye (B). The ELM, EZ, and CIZ appeared fragmented and thin and the foveal bulge was not visible at 1 month after surgery (C). Progressive increases in the reflectivity of the outer bands along with reconstitution of the foveal bulge were observed between postoperative months 3 and 12. The reflectivity of the outer bands became similar to the corresponding unaffected eye at 12 months postoperatively, however the thickness of the outer bands remained thin compared to the corresponding unaffected eye (C).

Figure 6. Representative SD-OCT image of an eye with thickening of the central fovea but no reconstitution of the foveal bulge after repair of macula-off RRD. Preoperative SD-OCT image of the macula with a visual acuity of 20/200 (A). The thickness and reflectivity of the outer bands was normal in the corresponding

unaffected eye (B). All retinal layers were thin, and the ELM, EZ, and CIZ bands were unintelligible at 1 month after surgery (C). Each retinal layer became thicker and ELM and EZ bands were observed to be partially reconstituted at 3 months after surgery. Each retinal layer became thicker at 12 months after surgery, with no difference in retinal layer thickness appears observed compared to the corresponding unaffected eye. However, EZ and CIZ were only partially reconstituted at the central fovea, with a visual acuity of 20/40.

Figure 7. Correlation between the time of first appearance of the foveal bulge and final BCVA. The time of first appearance of the foveal bulge was not found to correlate with LogMAR at 12 months after surgery. logMAR, logarithm of the minimum angle of resolution.

Figure S1. Regression line for logMAR over time in 2 cases (A). Regression line for EZ-RPE over time in 2 cases (B). The slope of the regression line for logMAR and the slope of the regression line for EZ-RPE for each case (C).

図 1

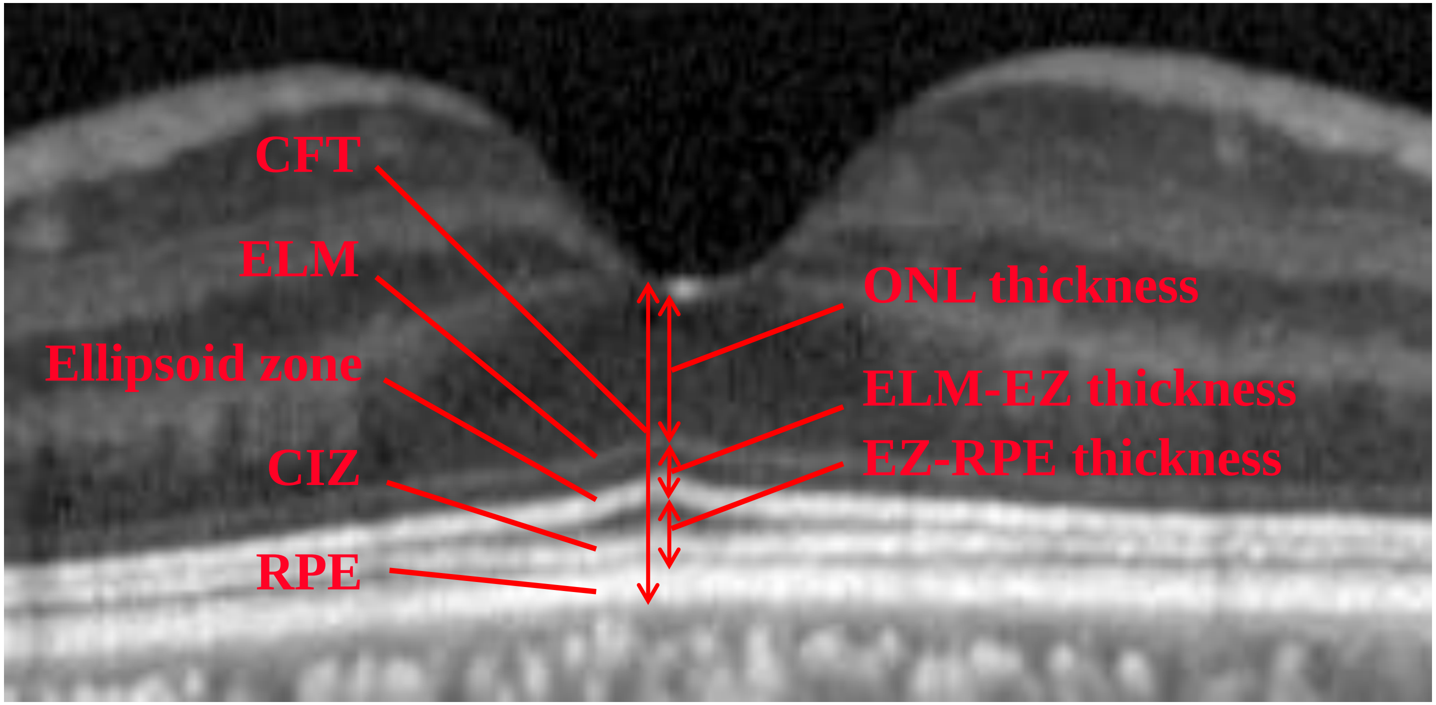
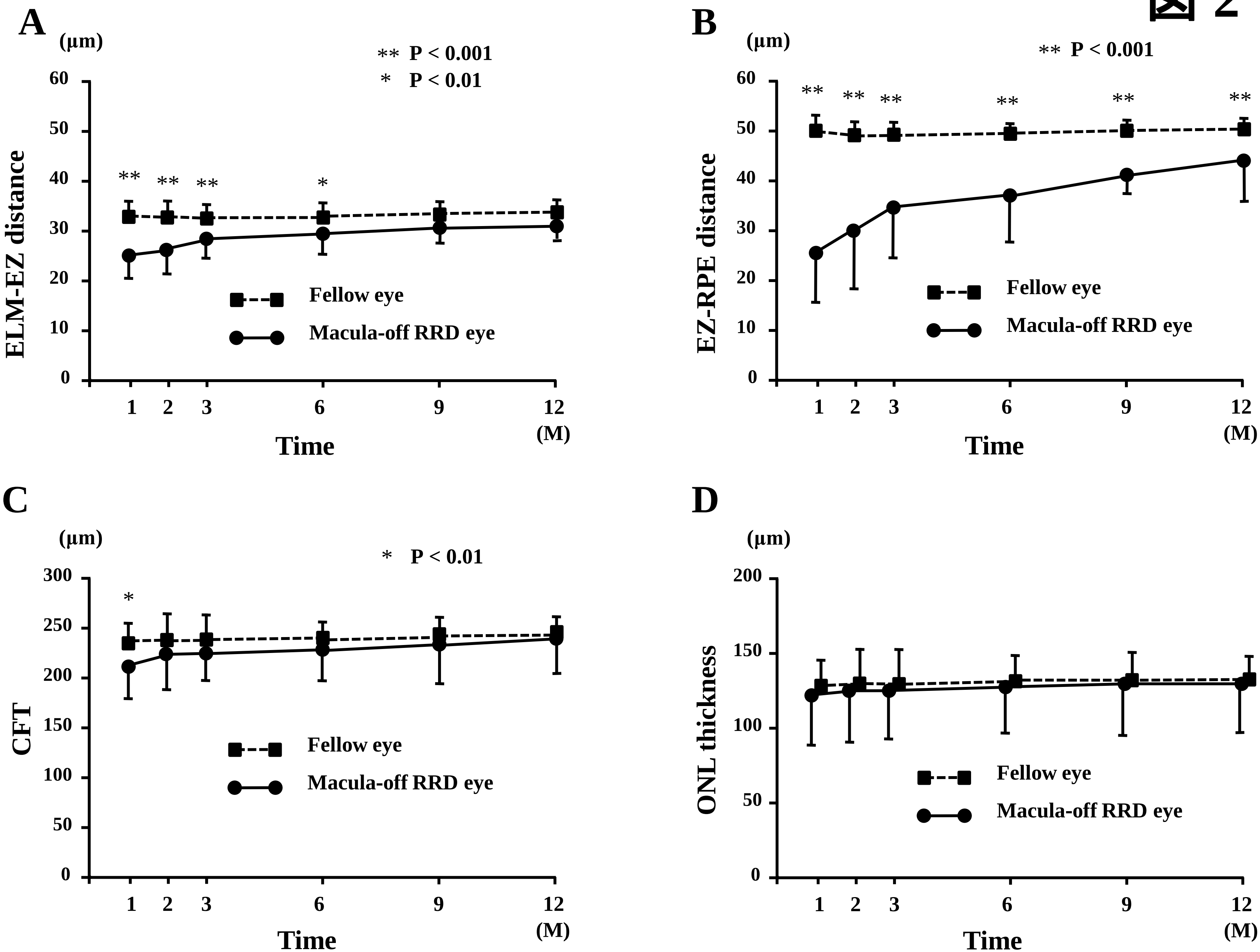

CFT
ELM
Ellipsoid zone
CIZ
RPE
ONL thickness
ELM-EZ thickness
EZ-RPE thickness

図 2



A
(µm)
** P < 0.001
* P < 0.01
ELM-EZ distance
Fellow eye
Macula-off RRD eye
Time
(M)
B
(µm)
** P < 0.001
EZ-RPE distance
Fellow eye
Macula-off RRD eye
Time
(M)
C
(µm)
* P < 0.01
CFT
Fellow eye
Macula-off RRD eye
Time
(M)
D
(µm)
ONL thickness
Fellow eye
Macula-off RRD eye
Time
(M)

図 3

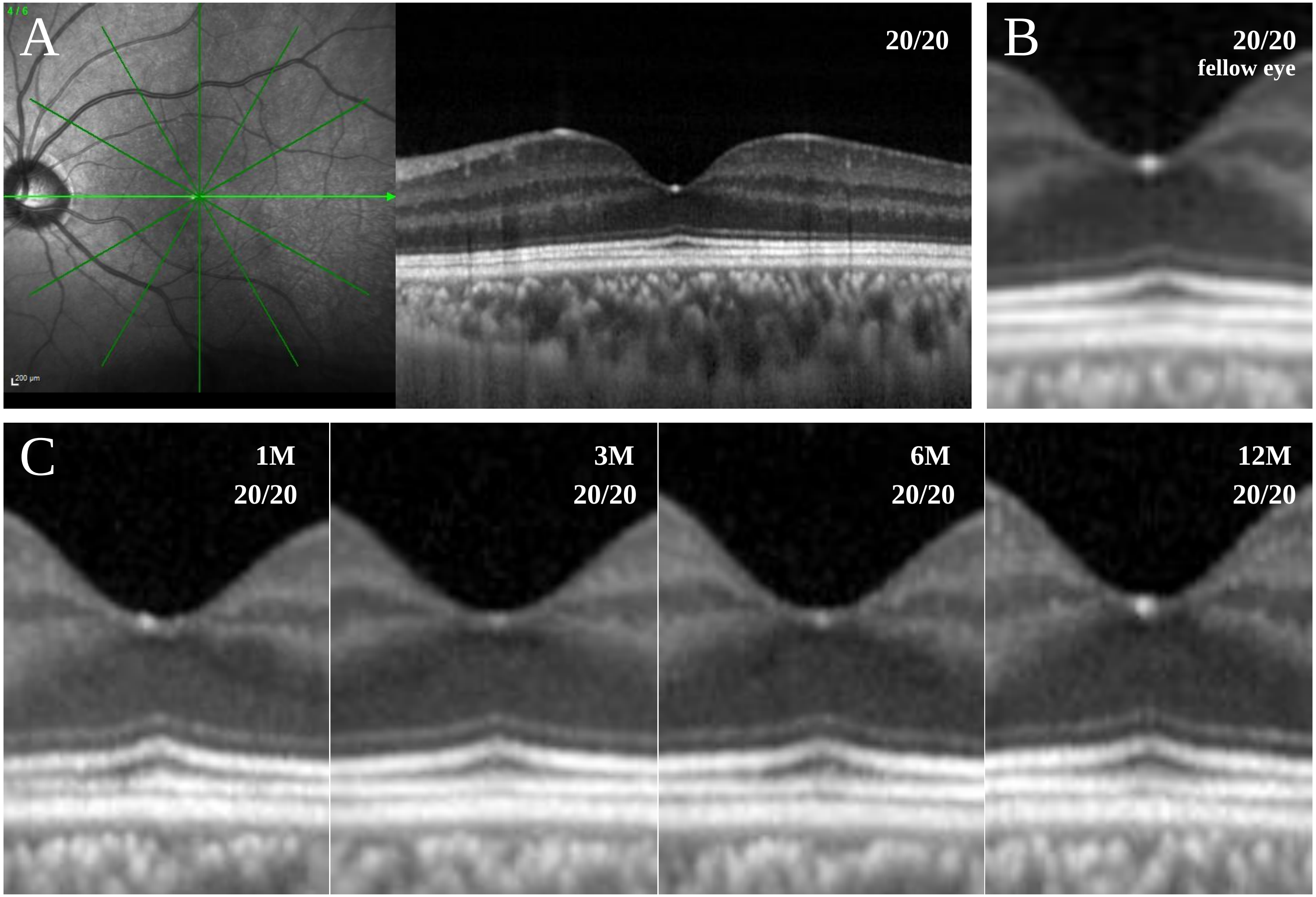
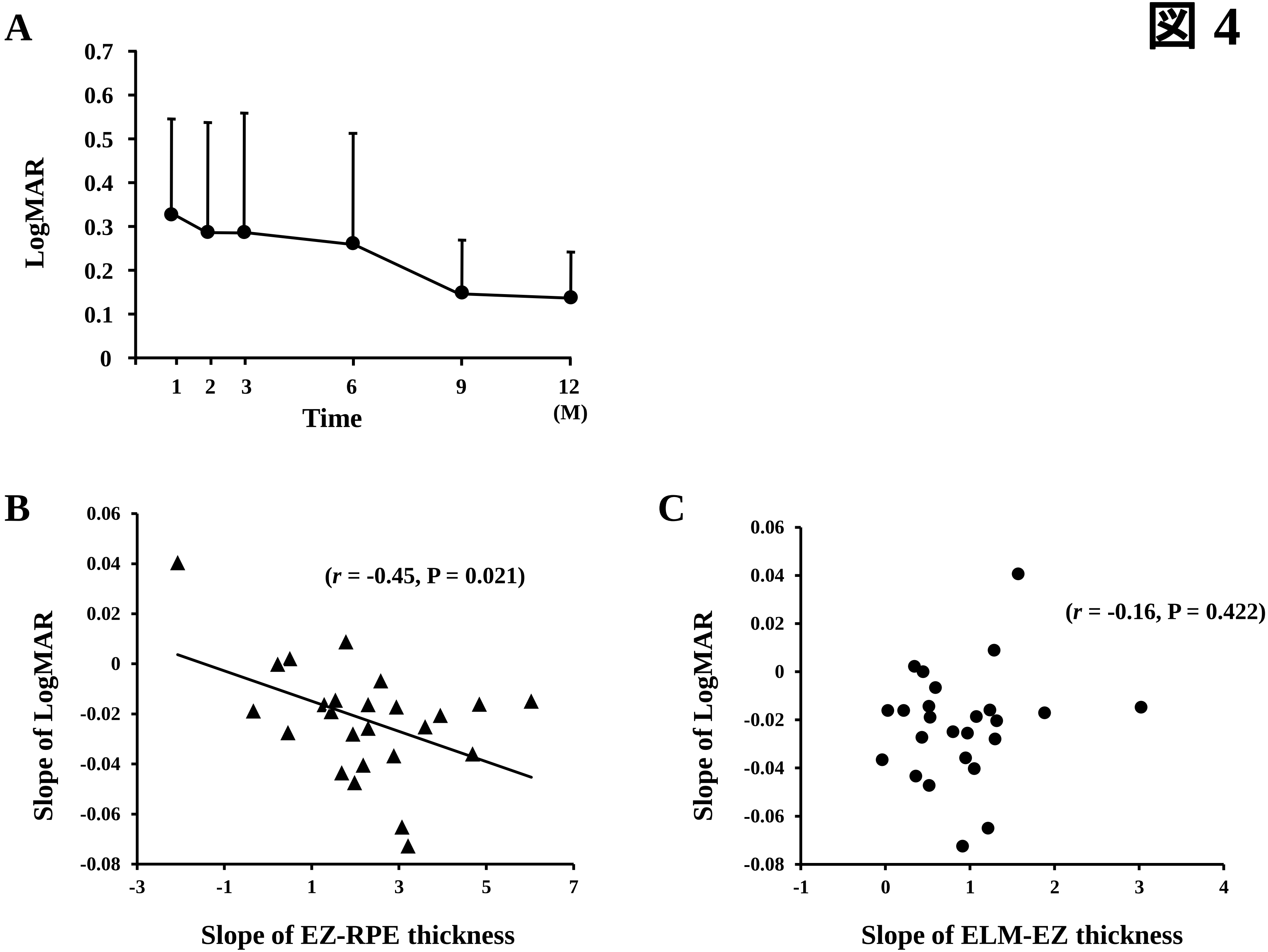


図 4



A
LogMAR
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
6
9
12
(M)
Time
B
Slope of LogMAR
(r = -0.45, P = 0.021)
0.06
0.04
0.02
0
-0.02
-0.04
-0.06
-0.08
-3
-1
1
3
5
7
Slope of EZ-RPE thickness
C
Slope of LogMAR
(r = -0.16, P = 0.422)
0.06
0.04
0.02
0
-0.02
-0.04
-0.06
-0.08
-1
0
1
2
3
4
Slope of ELM-EZ thickness

図 5

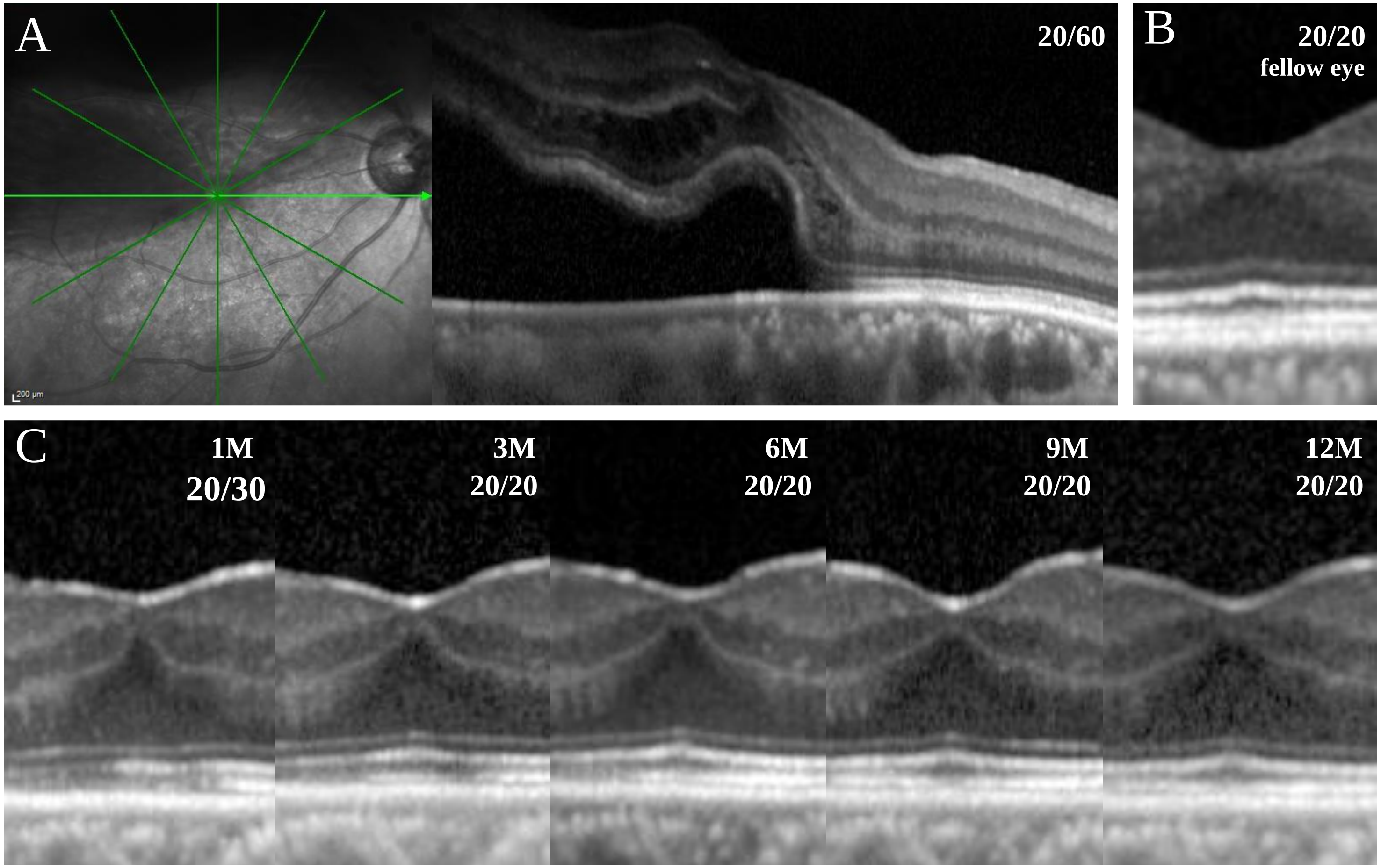

A
20/60
B
20/20
fellow eye
C
1M
20/30
3M
20/20
6M
20/20
9M
20/20
12M
20/20

図 6

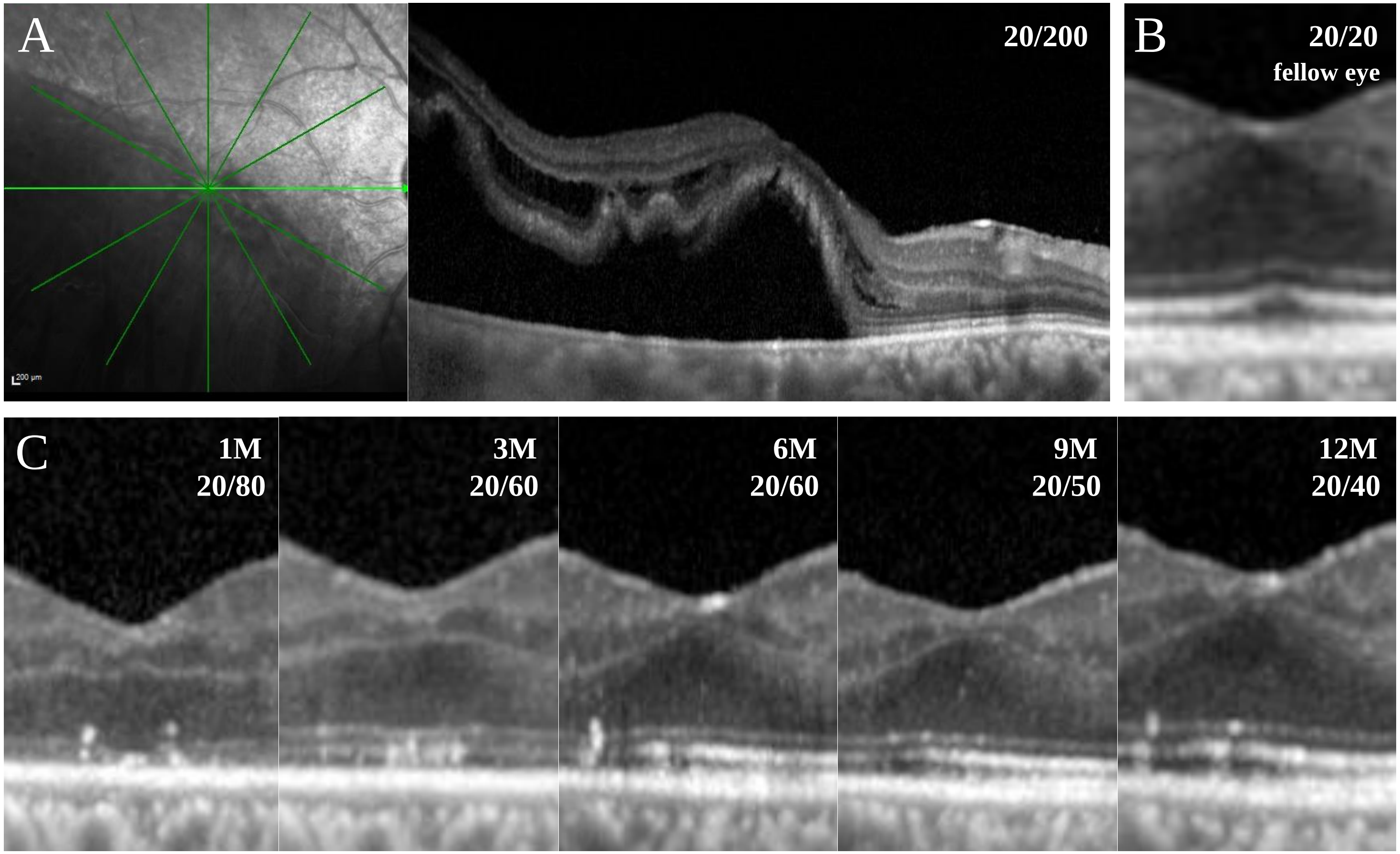

A
200 μm
20/200
B
20/20
fellow eye
C
1M
20/80
3M
20/60
6M
20/60
9M
20/50
12M
20/40

図 7

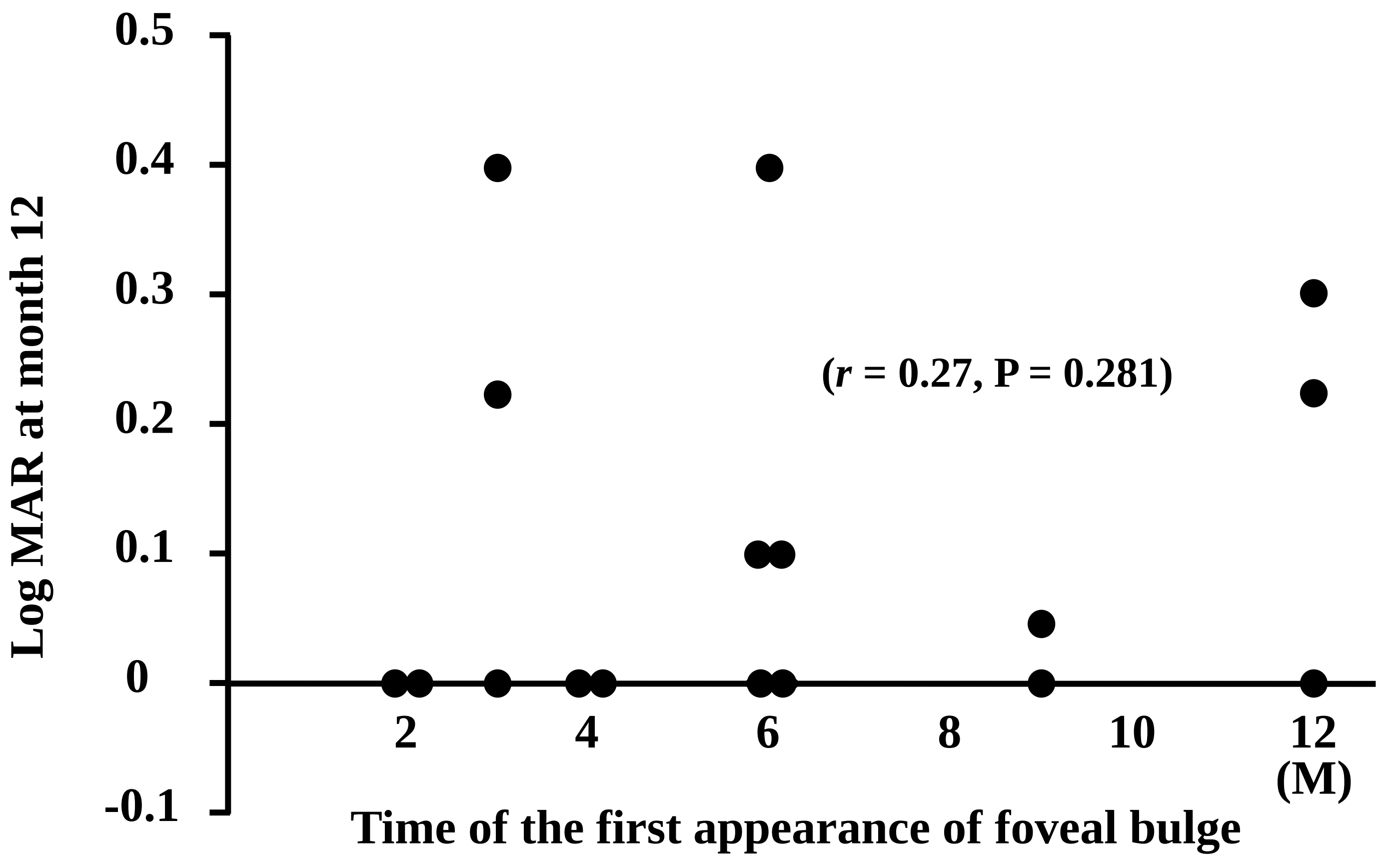

0.5
0.4
0.3
0.2
0.1
0
-0.1
Log MAR at month 12
(r = 0.27, P = 0.281)
2
4
6
8
10
12
(M)
Time of the first appearance of foveal bulge

表 1. Patient clinical characteristics

Characteristic	Macula-off	Macula-on	*P* Value
n	29	13	-
Age (years)	60.4 ± 12.2	60.0 ± 8.8	0.855
Sex (male/female)	20/9	10/3	0.598
LogMAR at the initial visit	1.13 ± 0.73	0.00 ± 0.93	< 0.001
Axial length (mm)	25.5 ± 1.8	26.0 ± 2.1	0.871
PPV/PPV+PEA+IOL	17/12	8/5	0.877

表 2. Change in the thickness of the different layers in eyes with macula-off or macula-on RRD

	Parameter	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	*P*-value
Macula-off	LogMAR	0.39 ± 0.29	0.35 ± 0.27	0.31 ± 0.27	0.27 ± 0.25	0.16 ± 0.14	0.15 ± 0.14	< 0.001
	CFT (μm)	212 ± 36	227 ± 41	228 ± 33	230 ± 35	236 ± 44	240 ± 34	0.413
	ONL thickness (μm)	122 ± 38	128 ± 41	126 ± 36	129 ± 34	133 ± 41	132 ± 35	0.977
	ELM-EZ thickness (μm)	25.2 ± 4.8	26.9 ± 4.3	28.8 ± 2.9	29.7 ± 3.8	30.7 ± 3.3	31.4 ± 2.6	< 0.001
	EZ-RPE thickness (μm)	25.4 ± 10.4	30.5 ± 12.2	35.0 ± 10.4	37.1 ± 9.9	40.0 ± 5.6	41.1 ± 5.6	< 0.001
Macula-on	LogMAR	0.01 ± 0.02	0.01 ± 0.03	0.01 ± 0.03	0.01 ± 0.03	0.04 ± 0.06	0.03 ± 0.05	0.885
	CFT (μm)	245 ± 24	242 ± 26	239 ± 30	248 ± 29	250 ± 22	251 ± 18	0.949
	ONL thickness (μm)	132 ± 26	128 ± 29	124 ± 31	132 ± 30	128 ± 17	135 ± 16	0.972
	ELM-EZ thickness (μm)	30.5 ± 4.0	31.8 ± 3.6	32.1 ± 3.0	32.8 ± 3.1	32.0 ± 4.2	33.7 ± 4.0	0.687
	EZ-RPE thickness (μm)	46.3 ± 5.0	47.5 ± 4.8	47.0 ± 5.7	46.0 ± 5.0	48.0 ± 2.6	50.1 ± 2.6	0.551

RRD: rhegmatogenous retinal detachment, LogMAR: logarithm of the minimum angle of resolution, CFT: central foveal thickness, ONL: outer nuclear layer, ELM: external limiting membrane, EZ: ellipsoid zone, RPE: retinal pigment epithelial

表 3. Results of multiple stepwise regression analysis for independence of factors contributing to final BCVA

Variable			
Dependent	Independent	β	p-value
Final BCVA	Foveal bulge	-0.741	< 0.001
	EZ-RPE thickness	-0.394	0.075
	Preoperative BCVA	0.243	0.090
	Age	0.159	0.284
	Axial length	0.080	0.587
	Duration of macular detachment	0.084	0.600

BCVA: best-corrected visual acuity, EZ: ellipsoid zone, RPE: retinal pigment epithelium

表 4. Patient clinical characteristics in eyes with or without the foveal bulge

Characteristic	**Foveal bulge (+)**	**Foveal bulge (-)**	***P* Value**
n	17	12	-
Age (years)	60.5 ± 14.9	60.2 ± 10.2	0.965
Sex (male/female)	11/6	10/2	0.269
Duration of macular detachment (days)	3.2 ± 3.6	6.4 ± 5.8	0.113
LogMAR before surgery	1.09 ± 0.74	1.18 ± 0.73	0.731
Axial length (mm)	25.5 ± 2.3	25.6 ± 1.6	0.876

表 5. Change in the thickness of the different layers in eyes with or without the foveal bulge in macula-off RRD

	Parameter	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	*P*-value
Foveal bulge (+)	LogMAR	0.23 ± 0.14$^{*\ a}$	0.17 ± 0.15$^{*\ a}$	0.16 ± 0.19$^{*\ a}$	0.12 ± 0.15$^{*\ a}$	0.05 ± 0.07$^{*\ a}$	0.05 ± 0.07$^{*\ a}$	0.035^{b}
	CFT (μm)	216 ± 40	227 ± 39	229 ± 34	236 ± 36	244 ± 42	247 ± 33	0.472
	ONL thickness (μm)	122 ± 40	123 ± 37	124 ± 35	132 ± 34	140 ± 40	138 ± 36	0.838
	ELM-EZ thickness (μm)	26.3 ± 4.1	27.3 ± 4.1	29.2 ± 2.5	30.1 ± 2.8	31.5 ± 2.7	31.3 ± 2.8	0.002^{b}
	EZ-RPE thickness (μm)	28.0 ± 8.6$^{\dagger\ a}$	35.4 ± 8.3$^{\dagger\ a}$	40.9 ± 6.1$^{*\ a}$	42.7 ± 5.2$^{*\ a}$	42.7 ± 2.9$^{\dagger\ a}$	46.3 ± 5.9$^{\ddagger\ a}$	< 0.001^{b}
	ELM band integrity (rank)	3.9	4	4	4	4	4	0.592
	EZ band integrity (rank)	3.3$^{*\ a}$	3.7$^{\ddagger\ a}$	3.8$^{\ddagger\ a}$	4	4	4	< 0.001^{b}
	CIZ band integrity (rank)	1.5$^{\dagger\ a}$	2$^{\dagger\ a}$	2.3$^{\ddagger\ a}$	2.8$^{*\ a}$	3.6$^{\ddagger\ a}$	3.5$^{*\ a}$	< 0.001^{b}
Foveal bulge (-)	LogMAR	0.64 ± 0.30$^{*\ a}$	0.60 ± 0.22$^{*\ a}$	0.54 ± 0.23$^{*\ a}$	0.48 ± 0.22$^{*\ a}$	0.39 ± 0.15$^{*\ a}$	0.29 ± 0.11$^{*\ a}$	0.053
	CFT (μm)	202 ± 22	228 ± 48	226 ± 35	220 ± 34	236 ± 65	230 ± 37	0.810
	ONL thickness (μm)	123 ± 34	142 ± 55	131 ± 40	123 ± 36	124 ± 56	125 ± 36	0.978
	ELM-EZ thickness (μm)	21.8 ± 5.5	25.8 ± 5.0	28.1± 3.4	29.2 ± 5.1	29.0 ± 4.2	32.0 ± 2.3	0.022^{b}
	EZ-RPE thickness (μm)	18.0 ± 12.7$^{\dagger\ a}$	19.8 ± 13.1$^{\dagger\ a}$	25.2 ± 8.6$^{*\ a}$	28.1 ± 8.9$^{*\ a}$	34.3 ± 6.0$^{\dagger\ a}$	34.8 ± 5.4$^{\ddagger\ a}$	0.051
	ELM band integrity (rank)	3.1	3.2	3.4	3.7	4	4	0.203
	EZ band integrity (rank)	2.1$^{*\ a}$	2.6$^{\ddagger\ a}$	3$^{\ddagger\ a}$	3.5	4	4	< 0.001^{b}
	CIZ band integrity (rank)	1$^{\dagger\ a}$	1.2$^{\dagger\ a}$	1.2$^{\ddagger\ a}$	1.5$^{*\ a}$	2$^{\ddagger\ a}$	1.6$^{*\ a}$	0.159

*p<0.001, ‡ p<0.01, † p<0.05. [a]Statistically significant difference is observed using unpaired *t*-test between in eyes with macula-off RRD group and macula-on RRD group at the each period. [b]Statistically significant difference is observed using one way analysis of variance to evaluate the change of each parameter with time.

RRD: rhegmatogenous retinal detachment, LogMAR: logarithm of the minimum angle of resolution, CFT: central foveal thickness, ONL: outer nuclear layer, ELM: external limiting membrane, EZ: ellipsoid zone, RPE: retinal pigment epithelial, CIZ: cone interdigitation zone