Restoration of Foveal Thickness and Architecture After Macula-Off Retinal Detachment Repair

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PURPOSE. To investigate the foveal changes after repair of macula-off rhegmatogenous retinal detachment (RRD).

METHODS. Prospective comparative case series. Twenty-four eyes of 24 patients with macula-off/fovea-on detachment (n = 9) and fovea-off detachment (n = 15) were studied. Serial optical coherence tomography (OCT) images taken at the same location were recorded at months 1, 3, 6, and 12 after operation. Fellow eyes were used as controls.

RESULTS. No significant changes of the central foveal thickness (CFT) were recorded in the fovea-on group over the follow-up. From month 1 to month 12, CFT increased significantly in the fovea-off group (P < 0.00001). In this group, a significant increase of the Henle fiber and outer nuclear layer (HFL + ONL, P = 0.007), external limiting membrane (ELM)-ellipsoid zone (EZ, P = 0.03), and EZ-retinal pigment epithelium (RPE) thicknesses (P < 0.00001) was recorded. Significant restoration of the integrity of the ELM in the fovea-off group (P < 0.001) and of the EZ and cone interdigitation zone in the fovea-on group and the fovea-off group was observed (P = 0.02 and P < 0.001, and P = 0.002 and P < 0.001, respectively). Twelve months after operation the foveal bulge restored in 8 of 15 eyes of the fovea-off group. Multiple regression analysis showed that in the fovea-off group BCVA correlated with EZ-RPE thickness at months 1 and 12, whereas the improvement of BCVA during the 12 months follow-up correlated with the increase of ELM-RPE thickness.

CONCLUSIONS. Optical coherence tomography scans taken serially at the same location showed a progressive increase of HNL+ONL, ELM-EZ, and EZ-RPE thicknesses and restoration of the integrity of outer retinal bands after repair of fovea-off RRD. The use of software able to rescan at exactly the same area is crucial to correctly follow and interpret the reconstitution of the retinal bands and to correlate them to BCVA recovery.

Keywords: rhegmatogenous retinal detachment, optical coherence tomography, foveal bulge, retinal regeneration, ellipsoid zone

Rhegmatogenous retinal detachment (RRD) starts a cascade of events that results in cellular changes throughout the retina.1–6 After reattachment, regeneration of outer segments (OS) of photoreceptors do occur, but often in a disorganized fashion.3 Abnormalities of the architecture of the retina and of the photoreceptor-retinal pigment epithelium (RPE) interface including shortening and misalignment of the cone OS and disorganization of the RPE apical processes may persist for years.7,8

With the introduction of spectral-domain optical coherence tomography (SD-OCT), an unprecedented visualization of in vivo retinal morphology has become possible, enabling the detection of microscopic abnormalities in the macula to histologic details.

According to the classification recently proposed by the International Nomenclature for Optical Coherence Tomography panel,9 the following seven bands/layers/zones can be recognized at the foveal center: the innermost one (layer no. 8), a hyporeflective zone between the vitreoretinal interface and the external limiting membrane (ELM), is composed of Henle’s fibre layer (HFL, inner half of the zone) and of the outer nuclear layer (ONL, outer half of the zone). The second hyperreflective band (layer no. 9) is the ELM. The third hyporeflective band (layer no. 10) has been attributed to the myoid zone of the photoreceptors, whereas the fourth hyporeflective band (layer no. 11) to the ellipsoid zone (EZ) of the photoreceptors; the fifth hyporeflective band (layer no. 12) represents the OS of the photoreceptors; the sixth hyporeflective zone (layer no. 13) represents the cone interdigitation zone (CIZ) with the RPE; the deepest, hyporeflective retinal band (layer no. 14) has been attributed to the RPE/Bruch’s membrane complex zone (Fig. 1).

Furthermore, at the central fovea, an upward deflection of the ELM, EZ, and CIZ, the so-called foveal bulge (FB) is visible in healthy eyes.

Previous studies have proposed that the integrity of the ELM, EZ (termed in the past as junction between the inner and outer segment [IS/OS] of photoreceptors), and of the CIZ (termed in the past cone outer segment tips [COST] line) along with the presence of FB correlates with visual acuity (VA)
METHODS

This prospective observational study included all the patients at the Eye Clinic of the University of Molise (Campobasso, Italy) between October 1, 2011 and December 1, 2012 that presented primary, macula-off RRD uncomplicated by proliferative vitreo-retinopathy (PVR) grade C or greater. The fovea status was confirmed by a preoperative SD-OCT scan at the macula. Patients were divided into two groups based on their preoperative macular and foveal status evaluated with OCT: (1) macula-off but fovea-on RRD, defined as a RD involving the macula but not the fovea (diameter of the physiologic fovea being 500 μm), and (2) fovea-off RRD, defined as an RD involving the fovea.

Preoperative data collection included a complete medical and ophthalmic history, logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) tested on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 m, characteristics of detachment, lens status, and time from the onset of symptoms suggestive of RRD to surgery.

Exclusion criteria included dense ocular media, preexisting macular conditions (e.g., AMD, vascular occlusive diseases, diabetes), and postoperative changes (e.g., subretinal fluid, macular edema, significant epiretinal membranes) that were likely to interfere with accurate evaluation of retinal layers. Also excluded were eyes with a refractive error more than −8.0 or +3.0 diopters (D) or patients with anisometropia exceeding 2 D of spherical equivalent. For pseudophakic eyes the refractive error present prior to cataract extraction was retrieved and used for calculations.

Follow-ups including repeated ophthalmologic examinations were scheduled at 1, 3, 6, and 12 months after the surgical procedure.

All subjects were treated in accordance with the Declaration of Helsinki. This study was approved by the institutional review board of the University of Molise. Informed consent was obtained from all the participants.

Imaging

Images were acquired with the Spectralis HRA+OCT, which combines a SD-OCT with a confocal scanning laser ophthalmoscope that provides a reference fundus image. The SD-OCT records up to 40,000 A-scans per second with an axial digital resolution of approximately 4 μm and a transversal digital resolution of approximately 15 μm in the high-resolution mode. The Spectralis simultaneously images the eye with two beams of light. One beam captures an image of the retina and maps over 1000 points to track eye movement. Using the mapped image as a reference, the second beam is directed to the desired location despite blinks or saccadic eye movements. This TruTrack dual beam technology creates a detailed retinal map each time a patient is imaged. It also mitigates eye motion artifacts and minimizes operator variability in follow-up scans. The AutoRescan feature uses this map to automatically place follow-up scans in precisely the same location as the baseline scan. Once a scan is marked for follow-up, the AutoRescan tool will find the desired location; this eliminates subjective operator placement and increases the clinician ability to...
TABLE 1. Variations of the Thickness of the Different Retinal Layers at the Fovea Through the Follow-Up Period

<table>
<thead>
<tr>
<th>Fovea-On</th>
<th>¼</th>
<th>9</th>
<th>Fovea-Off</th>
<th>¼</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo 1</td>
<td>0.08 ± 0.07</td>
<td>0.08 ± 0.07</td>
<td>0.08 ± 0.07</td>
<td>0.08 ± 0.07</td>
<td>0.08 ± 0.07</td>
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<tr>
<td>Mo 3</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
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<tr>
<td>Mo 6</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
</tr>
<tr>
<td>Mo 12</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.03</td>
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</table>

* Values in bold are statistically significant.

The first postoperative SD-OCT scanning was conducted at 30 days after operation and used as a reference for all subsequent scans taken at months 3, 6, and 12. The central scanning line was carefully placed and centered on the fovea. The protocol consisted of a sequence of 97 horizontal sections that covered an area of 30° horizontally and 20° vertically recorded in the high-resolution mode (1536 A-scans) with a distance of approximately 60 μm between individual sections. Sixteen frames were acquired for each B-scan location to reduce noise and to improve image quality.

To measure the foveal central thickness (FCT), the OCT image with both the steapest foveal excavation and the highest foveal bulge (if visible) from the horizontal scans across the foveal area, was chosen. Foveal central thickness and central 1-mm subfield thickness were measured automatically by the software from the inner border of the internal limiting membrane (ILM) to the outer border of the RPE-Bruch’s membrane complex. Thickness of HFL + ONL, thickness of the distance between ELM and EZ and between EZ and RPE-Bruch’s membrane, were measured manually on the same selected central foveal scan throughout the follow-up using the computer-based caliper measurement tool in the SD-OCT system. HFL + ONL thickness was defined as the distance between the inner border of the ILM (at the steapest part of the foveal excavation) and the inner border of the ELM line in correspondence with the highest part of the foveal bulge (if visible).

External limiting membrane–EZ and EZ-RPE distances were also measured at the foveal bulge (if visible). In the absence of a visible foveal bulge, the measurements were performed along the vertical line passing through the steapest part of the foveal excavation and perpendicular to the RPE layer.

The integrity of the foveal ELM, EZ, and the CIZ was judged for each image according to a scale ranging from 1 to 4 on a 1-mm-diameter area (1 = no disruption; 2 = line disruption > 200 μm; 3 = line disruption < 200 μm; 4 = continuous line). The same measurements were taken in the fellow eyes at each follow-up visit and served as controls.

All OCT evaluations and measurements were performed by two retinal specialists (DG and MF) who were masked to VAs of the study participants. The average of two measures was then calculated. When there was disagreement, a third investigator (RD) who was also masked to VA of the study participants was consulted for the final decision.

**Statistical Analysis**

Statistical analysis was performed using statistical software (SPSS version 13.0; SPSS, Inc., Chicago, IL, USA).

The interrater agreement was compared using a weighted κ-coefficient: κ of 0.01 to 0.20 was considered to have slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 1.0 almost perfect agreement. A κ less than zero was considered to have no agreement.

The Friedman test was used for testing the differences among the measures taken during the follow-up. The Mann-
Whitney U test was used for comparison between study and fellow eyes. Multivariate regression analysis was performed to evaluate the parameters correlating to postoperative VA. To reduce the variables for the multiple regression analysis, bivariate correlation analysis between the variables BCVA, HFL + ONL, ELM-EZ, and EZ-RPE was performed using Pearson correlation analysis. Subsequently, stepwise multiple regression analysis was used to determine which independent variables (HFL + ONL, ELM-EZ, and EZ-RPE) best-predicted BCVA. The coefficient of determination R², corresponding to the percentage of BCVA variation explained by the independent variables using a best-fit regression line, was used to measure how well the variation in retinal layers thickness explained the variation in BCVA. The significance of the trend of the linear regression was determined by t-test. The presence of multicollinearity among independent variables (which may have obscured the correlation results) was tested by measuring the variance inflation factor (VIF) index which was expected to stay above 3 if multicollinearity problems were present. A value of P less than 0.05 was considered statistically significant.

RESULTS
Between October 1, 2011 and December 1, 2012, 126 patients underwent 25-G pars plana vitrectomy (Constellation; Alcon Labs, Fort Worth, TX, USA), transscleral cryopexy, or laser around the breaks and 20% sulfur hexafluoride gas injection at our department for the repair of macula-off RRD. Of these, 102
Progressive thickening of the fovea and restoration of the integrity of the outer bands after repair of fovea-off retinal detachment. (A) Fifteen days after operation the central foveal thickness (CFT) is 99 μm and no distinct outer bands are visible at the fovea. Visual acuity is 0.9 logMAR. (B) At 1 month postoperatively, the ELM and the EZ are disrupted but visible in the central part of the fovea. The CIZ is not visible. Central foveal thickness is 156 μm and VA is 0.7 logMAR. (C) At month 2, the HFL + ONL have thickened, and the reflectivity of ELM and EZ is more distinct at the fovea. Central foveal thickness is 182 μm and VA is 0.6 logMAR. (D) At month 3, HFL + ONL have further thickened and the ELM and EZ are better delineated. Central foveal thickness is 196 μm and VA is 0.4 logMAR. (E) At month 6 the CIZ becomes visible. Central foveal thickness is 219 μm and VA remains 0.4 logMAR. (F) At month 9, the CIZ line is more evident. Central foveal thickness is 224 μm and VA is 0.3 logMAR. (G) At month 12 the retinal architecture at the fovea is almost normal and the outer bands appear continuous. Central foveal thickness is 236 μm and VA is 0.3 logMAR. The FB is not visible. (H) In the fellow eye the CFT measures 233 μm, the outer retinal bands appear thicker in comparison to the study eye and the FB is present. Visual acuity is 0 logMAR.

were excluded for the following reasons: presence of PVR grade C or worse (n = 18), previous vitreo-retinal surgery (n = 21), macular diseases (n = 10), postoperative development of dense cataract (n = 14), macular edema (n = 8), subretinal fluid (n = 7), or significant epiretinal membrane (n = 8) at any time of follow-up, and incapacity of attend regularly the follow-up visits (n = 15).

In the end, nine eyes with fovea-on detachment and 15 eyes with fovea-off detachment were studied. The male to female ratio was 6.3 and 8.7 in the fovea-on and fovea-off group, respectively.

Mean age ± SD was 56.5 ± 7.7 and 58.2 ± 6.4 years in the fovea-on and in the fovea-off group, respectively. In the fovea-on group five eyes were phakic and four were pseudophakic, whereas in the fovea-off group five eyes were phakic and 10 were pseudophakic. Mean refractive error ± SD (range) in the study eyes and in the fellow eyes was −4.3 ± 3.9 (−8.0 to 0.25) and −4.1 ± 3.1 (−7.75 to 0.5) in the fovea-on group, and −3.8 ± 3.4 (−8.0 to 1.5) and −3.5 ± 3.2 (−8.0 to 1.5) in the fovea-off group, respectively. No significant difference between study and fellow eyes was found in either group.

Over the follow-up from months 1 to 12, BCVA improved significantly only in the fovea-off group, from 0.5 ± 0.2 to 0.5 ± 0.3 (P = 0.00008; Table 1). Similarly CFT and 1-mm central subfield thickness increased significantly only in the fovea-off group. In this group, a significant increase of thickness was documented at the level of HFL + ONL (from 109.0 ± 25.5–128.0 ± 28.5, P = 0.007), of the ELM-EZ distance (from 17.5 ± 11.3–26.5 ± 3.9, P = 0.03) and of EZ-RPE distance (from 26.8 ± 16.5–51.3 ± 7.7, P < 0.00001) from months 1 to 12 (Figs. 2–5). Concomitantly, significant restoration of the integrity of the ELM in the fovea-off group (P < 0.001) and significant restoration of the EZ (P = 0.02 and P < 0.001, respectively) and CIZ (P = 0.002 and P < 0.001, respectively) in the fovea-on group (Fig. 6) and the fovea-off group were observed (Table 1).

The overall percentage of agreement was greater than 94% for both ELM and EZ, with an interrater agreement of κ = 0.9 and 0.86, respectively, whereas interrater agreement for CIZ was κ = 0.78.

Foveal bulge was visible in all eyes of the fovea-on group and in none of the eyes of the fovea-off group at the 1-month assessment. However, during the follow-up, FB showed a tendency to reform and 12 months postoperatively was appreciable in 8 of 15 eyes of the fovea-off group, although it was less pronounced if compared with the fellow eyes. Mean duration of detachment (±SD, range) was not significantly different between the eyes with visible bulge (7.3 ± 5.4 [3–20] days) and the eyes without visible bulge at month 12 (12.4 ± 9.2 [6–30] days). Mean VA (±SD) was 0.17 ± 0.16 and 0.51 ± 0.26 in the group with and without bulge, respectively, at month 12. The difference was statistically significant (P = 0.009; Figs. 2–5).
In the comparison with the fellow eye, a significant difference was found for the HFL+ONL thickness throughout the duration of the follow-up (HFL+ONL greater in the operated eye) in the fovea-on group. \((P = 0.01, \text{Table 2; Fig. 6})\).

Conversely, the eyes with fovea-off detachments showed significantly lower values in the operated eye for HFL+ONL, ELM-EZ, and EZ-RPE thicknesses at month 1. At month 12 such differences became not significant with the exception of the EZ-RPE thickness \((P = 0.03; \text{Table 2})\).

Multivariate regression analysis showed that BCVA did not correlate to HFL+ONL thickness \((P > 0.05 \text{ at months 1 and 12})\); conversely, BCVA correlated to ELM-EZ at month 1 (Pearson’s coefficient \(= -0.753, P < 0.01\)), but not at month 12 (Pearson’s coefficient \(= -0.06, P = 0.78\)) and correlated with EZ-RPE both at months 1 and 12 (Pearson’s coefficient \(= -0.817, P < 0.01\) and \(-0.582, P = 0.003\), respectively, Fig. 7).

To select the best regression model the stepwise method was employed (the analysis pertain to the data of the first month). The resulting models are shown in Table 3. Multicollinearity statistics (VIF) were below 3, excluding collinearity problems in the model. Most of the variance of BCVA could be explained by EZ-RPE alone (model 1, correlation coefficient \(= -0.8\)). Using also the ELM-EZ as predictor (model 2), more than 90% of the variance of BCVA could be predicted using the following formula:

\[
\log_{10} \text{MAR BCVA} = 0.85 - 0.007 \times \text{EZ} - \text{RPE} - 0.012 \\
\times \text{ELM-EZ}. \tag{1}
\]

The HFL+ONL thickness was not significantly correlated with the BCVA and therefore was not included in the regression model.

To further test the dependence of BCVA on ELM-EZ and EZ-RPE, we also evaluated the regression between the BCVA improvement and the increased thickness of retinal layers during the 12 months of follow-up. The hypothesis was that the modification of ELM-EZ and EZ-RPE thickness over time should be accompanied by a modification in BCVA.

The Pearson’s correlation index showed that the increase of ELM-EZ and EZ-RPE thicknesses, singularly taken, did not correlate to BCVA improvement. However, significant correlation was found between the improvement of BCVA and the increase of ELM-RPE thickness \((\text{ELM-EZ} + \text{EZ-RPE thickness})\) during the 12 months follow-up \((\text{Pearson} = -0.444; P = 0.03)\). The best regression model obtained with the stepwise algorithm was the following:

\[
\text{improvement in BCVA} = -0.013 - 0.004 \times \text{increase in ELM-RPE thickness.} \tag{2}
\]

**DISCUSSION**

To the best of our knowledge this is the first prospective study using a SD-OCT technology capable of scanning the same retinal area to serially investigate the variation of thickness of retinal layers and the integrity of the outer retinal bands at the fovea following repair of macula-off RRD. Evolutionary changes observed postoperatively were substantial in the eyes with...
fovea-off detachments. In these eyes, we noted a progressive increase in the thickness of all central retinal layers along with partial restoration of the integrity of the outer retinal bands. Improvement of VA paralleled these changes and correlation between improvement of BCVA and increase of ELM-RPE distance over the 12-month follow-up was found.

Recently, as we have gained the technological advantages of SD-OCT, which allows for detailed retinal evaluation, our understanding of the foveal microstructure recovery process after RRD has broadened.

Most previous studies on this topic focused on the integrity of the outer retinal bands at the fovea, and investigated the correlation between the integrity of these bands and the values of VA after surgery. It has been proposed that alterations occurring at the level of the EZ (termed in the past as IS/OS junction) may be reversible and that the integrity of ELM may be a prerequisite in predicting subsequent EZ restoration and VA recovery. Conversely, persistent or worsening EZ disruption may be associated with progressive vision deterioration.

There are some important limitations intrinsic to the methodology used in these previous studies including their retrospective design and the qualitative evaluation of the OCT findings.

As far as the qualitative assessment of the lines on OCT scans is concerned, it should be considered that the reflectivity of a band may be reduced either because of fragmentation or because of thinning of the band itself. Both fragmentation and thinning, without other concomitant morphologic alterations, should be regarded with caution as an abnormality. In fact ELM, EZ, and CIZ bands may appear fragmented or even absent in healthy eyes as a result of artifacts. However, pure qualitative evaluation of the integrity of a band provides scarce information and should always be accompanied by concomitant evaluation of the thickness of the layers bordering the line to formulate accurate conclusions.

Therefore, pure qualitative evaluation of the integrity of a band provides scarce information and should always be accompanied by concomitant evaluation of the thickness of the layers bordering the line to formulate accurate conclusions.

For these reasons we decided to study the recovery of the retina not only qualitatively but also quantitatively by measuring the variations of thickness of the bands composing the fovea. In addition we compared the results obtained in the study eyes with those of the fellow eyes (with similar refractive characteristics) in order to study the progression toward "normality" of the operated eyes over a 12-month period.

We found that 1 month after operation the fovea was significantly thinned in the eyes with fovea-off detachments. Over the follow-up the central foveal thickness increased, with
A progressive thickening observed at the level of the HFL + ONL, ELM-EZ, and EZ-RPE distances. Interestingly the EZ-RPE distance (i.e., the space comprising the outer segment of the photoreceptors and the interdigitation between photoreceptors and RPE) almost doubled from months 1 to 12, and progressively approached the values recorded in the fellow eyes.

The increased length of the outer segments of photoreceptors at the fovea was also shown by the reconstitution, in some eyes, of the FB. Consistently with previous observations, we found that 1 month after operation, the FB was visible in all eyes with fovea-on detachment and in none of the eyes with fovea-off detachment. However, 12 months after operation, the FB became appreciable in 8 of 15 eyes with fovea-off detachment.

### Table 2. Comparison Between Study and Fellow Eyes Throughout the Follow-Up Period

<table>
<thead>
<tr>
<th></th>
<th>Fovea-On</th>
<th></th>
<th>Fovea-Off</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Eye</td>
<td>Fellow Eye</td>
<td></td>
<td>Study Eye</td>
<td>Fellow Eye</td>
</tr>
<tr>
<td></td>
<td>n = 9</td>
<td></td>
<td>n = 15</td>
<td>n = 15</td>
</tr>
<tr>
<td><strong>1-mm central area thickness, µm, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mo 1</td>
<td>287.7 ± 17.8</td>
<td>282.2 ± 22.4</td>
<td>0.2</td>
<td>243.7 ± 42.1</td>
</tr>
<tr>
<td>Mo 3</td>
<td>288.4 ± 15.9</td>
<td>282.4 ± 21.9</td>
<td>0.2</td>
<td>249.8 ± 30.4</td>
</tr>
<tr>
<td>Mo 6</td>
<td>289.7 ± 16.9</td>
<td>282.9 ± 22.2</td>
<td>0.1</td>
<td>266.3 ± 23.9</td>
</tr>
<tr>
<td>Mo 12</td>
<td>288.7 ± 15.7</td>
<td>282.7 ± 22.7</td>
<td>0.2</td>
<td>280.1 ± 23.6</td>
</tr>
<tr>
<td><strong>CFT, µm, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mo 1</td>
<td>229 ± 21.2</td>
<td>223.1 ± 20.4</td>
<td>0.1</td>
<td>183.0 ± 49.6</td>
</tr>
<tr>
<td>Mo 3</td>
<td>225.3 ± 21.3</td>
<td>223.4 ± 21.3</td>
<td>0.5</td>
<td>194.2 ± 36.5</td>
</tr>
<tr>
<td>Mo 6</td>
<td>226 ± 21.1</td>
<td>223.7 ± 20.8</td>
<td>0.4</td>
<td>212 ± 35.9</td>
</tr>
<tr>
<td>Mo 12</td>
<td>225.4 ± 22.1</td>
<td>223.8 ± 21.4</td>
<td>0.5</td>
<td>226.7 ± 33.3</td>
</tr>
<tr>
<td><strong>HFL + ONL thickness, µm, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mo 1</td>
<td>117.9 ± 26.9</td>
<td>109.7 ± 25.2</td>
<td>0.01</td>
<td>109.5 ± 25.5</td>
</tr>
<tr>
<td>Mo 3</td>
<td>118.9 ± 24.9</td>
<td>109.1 ± 26.1</td>
<td>0.01</td>
<td>106.5 ± 28</td>
</tr>
<tr>
<td>Mo 6</td>
<td>119.1 ± 23.2</td>
<td>110 ± 26.3</td>
<td>0.01</td>
<td>118.3 ± 28.6</td>
</tr>
<tr>
<td>Mo 12</td>
<td>123 ± 29.0</td>
<td>110.2 ± 25.9</td>
<td>0.01</td>
<td>128.2 ± 28.5</td>
</tr>
<tr>
<td><strong>ELM-EZ thickness, µm, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mo 1</td>
<td>25.2 ± 6.5</td>
<td>29.0 ± 3.7</td>
<td>0.3</td>
<td>17.5 ± 11.3</td>
</tr>
<tr>
<td>Mo 3</td>
<td>24.4 ± 4.0</td>
<td>28.7 ± 4.1</td>
<td>0.65</td>
<td>24.4 ± 4.6</td>
</tr>
<tr>
<td>Mo 6</td>
<td>26.2 ± 5.2</td>
<td>28.6 ± 4.6</td>
<td>0.008</td>
<td>23.5 ± 4.7</td>
</tr>
<tr>
<td>Mo 12</td>
<td>28 ± 5.3</td>
<td>28.9 ± 4.3</td>
<td>0.65</td>
<td>26.3 ± 3.9</td>
</tr>
<tr>
<td><strong>EZ-RPE thickness, µm, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mo 1</td>
<td>68.1 ± 11.3</td>
<td>60.2 ± 5.5</td>
<td>0.008</td>
<td>26.8 ± 16.5</td>
</tr>
<tr>
<td>Mo 3</td>
<td>67.8 ± 12.8</td>
<td>60.9 ± 5.6</td>
<td>0.09</td>
<td>45.4 ± 10.6</td>
</tr>
<tr>
<td>Mo 6</td>
<td>69 ± 13.7</td>
<td>60.8 ± 5.3</td>
<td>0.1</td>
<td>50.4 ± 9.9</td>
</tr>
<tr>
<td>Mo 12</td>
<td>68.9 ± 11.0</td>
<td>61.3 ± 5.8</td>
<td>0.1</td>
<td>51.3 ± 7.7</td>
</tr>
</tbody>
</table>

Values in bold are statistically significant. * Mann-Whitney U test.
The length of the outer portion of the photoreceptors (EZ-RPE distance) correlated with BCVA at months 1 and 12 and VA was significantly better in the subgroup with reconstitution of the foveal bulge.

Our results are consistent with histology studies that show photoreceptor OS are greatly shortened and misaligned in a region of detachment but may regrow and recover their shape, at least partially, after reattachment. Our results are consistent with histology studies that show photoreceptor OS are greatly shortened and misaligned in a region of detachment but may regrow and recover their shape, at least partially, after reattachment.

It is important to note that the values we measured in the fellow, healthy eyes are in line with previous histologic studies of the human retina and OCT-based works, including normative macular thickness data obtained using the OCT Spectralis, (i.e., the instrument used in the present study). These works showed that the mean length of the OS of photoreceptors in the fovea of healthy individuals measures approximately 50 μm. Progressive increase of central retinal thickness was accompanied by restoration of the integrity of the outer retinal bands. Interestingly, we noted that ELM may reconstitute over time, and regions devoid of both ELM and EZ at an early stage after reattachment may appear nearly normal 12 months after operation.

These results apparently challenge the assumptions that the lack of visualization of the ELM line on SD-OCT is a sign of irreversible damage or loss of photoreceptor nuclear body after RRD repair; however, it is possible that we failed to visualize the ELM in the early postoperative period because...
its thickness was below the capacity of resolution of the SD-OCT device we used (i.e., ELM present but extremely thin and thus not visible). If this is the case, the progressive thickening of the ELM (and thus its visualization) during the course of the follow-up could have been erroneously interpreted as a regeneration.

Interestingly we observed that when an apparently complete ELM regeneration occurred, it usually happened in the first 6 months after operation. Conversely, if ELM defects persisted for more than 6 months after surgery, the chances of subsequent recovery were very few. Therefore, according to our results and given the current OCT technology, the assumption of previous studies proposing that “lack of ELM = irreversible damage of photoreceptors” might be true but should not be applied to the images taken in the early postoperative period. On the other hand, we observed that apparent reconstitution of the integrity of the outer bands is not always accompanied by a full recovery of VA. Whether this is due to malfunctioning photoreceptors or to reparative processes mediated by other types of cells (apparently restoring the architecture of the outer bands but not working as photoreceptors) remains to be elucidated.

Similarly to the outer foveal layers, the HFL + ONL thickness at the fovea progressively increased to values similar to those of the fellow eyes. The reduced HFL + ONL thickness in the early postoperative period may be due to migration of cone cell bodies from the outer border to the middle of this layer observed in response to detachment.28 After reattachment, the recovery of cones along with Müller cell proliferation and hypertrophy may be responsible for the reconstitution of the normal HFL + ONL thickness.29

Differently from the fovea-off group, in the fovea-on group the HFL + ONL was significantly thicker in comparison to that of fellow eyes throughout the follow-up. It is possible that the increased HFL + ONL thickness in these eyes was the result of subtle edema devoid of cysts, not causing substantial abnormalities of reflectivity and thus difficult to distinguish from adjacent normal, nondematous tissue. This might be especially true for the Henle's fibers portion of the HFL + ONL layer that is extremely thin at the central fovea and whose visualization strongly depends on the entry position of the SD-OCT beam through the pupil.

Another explanation is that exuberant reactive processes may overcome the entity of the injury caused by detachment, and may result in increased postoperative thickness in areas close to but not directly involved by the detachment. In fact, the foveal damage (and consequential reparative processes) in the case of a macula-off/fovea-on detachment may be underestimated.10,30

Indeed, we observed that in the early postoperative period some irregularities of the EZ and CIZ bands at the fovea were often visible in the eyes with fovea-on detachments. However, we do acknowledge that since the macula was detached in all these cases, subretinal fluid might have reached the fovea during operation or may have been displaced by intraocular gas into the fovea region in the postoperative period, resulting in a foveal detachment of short duration with subsequent changes.

Limitations of this study include the relatively small sample size, the follow-up limited to 12 months, and the fact that patients with quite common postoperative complications like epiretinal membrane and intra/subretinal fluid were excluded. However, restrictive inclusion criteria were necessary in order to precisely identify the retinal layers boundaries and to minimize the chance of recording increased thicknesses as a consequence of edema or anteroposterior traction due to epiretinal membranes. Another limitation of the study is that some retinal distances were manually measured. However, a software allowing for automated calculations of the retinal layers with the Spectralis was not available when our study started. Furthermore, a reliable, purely automated calculation of retinal thicknesses might be difficult to achieve in eyes where the outer retinal bands appear absent or severely fragmented and retinal layers are distorted and not clearly distinguishable, as it usually happens in early phases after fovea-off detachment repair.

Strengths of the study include its prospective design, the use of an OCT device that is able to record serially images at the same location, and the quantitative analysis of the retinal layers.

In conclusion, this study shows that progressive recovery of thickness and restoration of the outer retinal layers/bands at the fovea occurs after fovea-off retinal detachment repair and may be accurately documented with OCT. Best-corrected VA correlates with EZ-RPE distance both at 1 and 12 months after RD repair, whereas BCVA improvement from month 1 to month 12 correlates with the increase of ELM-RPE thickness from months 1 to 12.

The use of modern software that allows rescanning at exactly the same area is crucial to correctly follow and interpret both the evolution of the foveal architectural changes and the reconstitution of the retinal layers/bands and to correlate them to VA recovery.

Acknowledgments

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