Topographic Changes of Retinal Layers after Resolution of Acute Retinal Detachment

Jae Hui Kim, Do Young Park, Hyo Shin Ha, and Se Woong Kang

PURPOSE. To investigate changes in thickness profiles of retinal layers after resolution of recent onset rhegmatogenous retinal detachment

METHODS. Spectral domain optical coherence tomography (SD-OCT) scans were performed for 28 patients diagnosed with unilateral inferior half or superior half retinal detachment who underwent retinal reattachment surgery. The thickness of each retinal layer was measured at 3000 μm and 2800 μm in the superior and inferior directions from the foveal center. The thicknesses of each retinal layer of the reattached retina were compared with those of the undetached region of the retina of the same eye.

RESULTS. Sixteen patients were diagnosed with superior half and 12 patients were diagnosed with inferior half retinal detachment. The mean duration of retinal detachment was 6.9 ± 3.9 days. SD-OCT scans were performed 10.4 ± 6.9 months after the surgery. The thicknesses of the outer nuclear layer and photoreceptor layer in the reattached retina were significantly thinner than those of the undetached retina (P = 0.012, and P = 0.018, respectively).

CONCLUSIONS. Our findings suggest that prominent retinal structural sequelae, especially in outer nuclear layer and photoreceptor layer, can be induced by a short duration of retinal detachment. Our findings also underscore the important role of initial retinal injuries that occur within the first several days on the long term structural prognosis. (ClinicalTrials.gov number, NCT01587794.) (Invest Ophthalmol Vis Sci. 2012;53:7316–7321) DOI:10.1167/iovs.12-10155

Surgical reattachment of a detached retina is the mainstay of treatment of rhegmatogenous retinal detachment (RRD). Experimental retinal detachment and reattachment models have demonstrated the recovery process of successfully reattached retinas, including reconfiguration and reorganization of the photoreceptor inner and/or outer segments,1–5 reorganization of photoreceptor-retinal pigment epithelium (RPE) interface,1,2 increased synaptic terminals in the outer plexiform layer (OPL),4 inhibition of glial cell proliferation,1,6 and recovery of normal distribution of proteins.4 These microscopic changes are thought to be the reason for visual function recovery following retinal reattachment.7–15 However, despite a high rate of successful anatomic reattachment, the recovery in visual function is often limited, even after a prolonged recovery period.16–19 This has been explained by the limited recovery of the retinal microstructure.1,2,4,14–19 Despite a few microscopic studies that revealed atrophy of the outer retinal layer and photoreceptor in the reattached human retina,14–19 the clinicopathologic correlation of the reattached retina, including quantitative analysis, has been limited because of a relative paucity of human material available for histopathologic analysis. Thus, most of studies that investigated the microstructure of reattached retinas have used animal models, and little is known about changes in reattached human retinas. Recent development in spectral domain optical coherence tomography (SD-OCT)13 allows more detailed retinal layer evaluation. Previous studies using SD-OCT have revealed abnormalities of retinal microstructure in reattached retina.14–19 However, these studies mainly focused on the photoreceptor layer (PRL) and/or external limiting membrane (ELM), although abnormalities of various retinal layers have been revealed in previous microscopic studies. In addition, qualitative rather than quantitative analysis was performed in most of the studies, and most importantly, all previous studies were observational and comparisons between the affected and normal control regions were not performed.

The current study involves a series of recent onset primary RRD that were managed with surgical retinal reattachment. We quantified the thickness of each retinal layer based on SD-OCT images and compared the thicknesses of reattached regions and undetached normal regions. The primary purpose of this study was to evaluate the changes in thickness profiles of each retinal layer in reattached retinas after acute RRD.

METHODS

This cross-sectional study was performed at the Samsung Medical Center according to the tenets of the Declaration of Helsinki. The study was approved by the institutional review board (Samsung Medical Center IRB No. 2010-06-030). Written informed consent was obtained from all patients before enrollment.

Patients who were diagnosed with unilateral RRD involving only the superior or inferior half of the retina, and who underwent successful scleral buckling procedure or vitrectomy by a single surgeon (SWK) between January 1, 2008 and August 1, 2011 were included in the study sample. Superior or inferior half retinal detachments were diagnosed based on fundus images that were taken just before the surgery. Retinal detachment involving the point of 1-disc-diameter distance, superior or inferior, from the foveal center of the detached region and preserving the point of 1-disc-diameter distance, superior or inferior, from the foveal center of the undetached region were defined as half retinal detachment (Fig. 1). Only patients who could estimate the time of onset of visual symptom of retinal detachment (sudden decrease in visual acuity or onset of visual field defect) accurately and were treated within 2 weeks of symptom onset were included.

Patients with any of the following conditions in either eye were excluded: traumatic retinal detachment, recurved retinal detachment, less than 6 months of follow up after surgery, insufficient cooperation

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for SD-OCT examination, media opacity that would preclude acquisition of clear SD-OCT images, −6.0 diopters (D) or more of spherical equivalent, prominent staphyloma, history of intraocular surgery other than cataract surgery or intraocular lens implantation, and other ocular diseases that may influence the macular microstructure. Additionally, individuals with indistinct intraretinal structure on SD-OCT images, large retinal vessels at the location of thickness measurement, or epiretinal membrane were excluded from result analysis.

Data collected included demographic characteristics, spherical equivalent of the fellow eye, visual acuity, location and extent of retinal detachment, duration of retinal detachment, number of retinal breaks, types of surgery, and duration between surgery and SD-OCT scan. Duration of retinal detachment was defined as the time between the onset of symptoms and the time of surgery. Visual acuities of counting finger and hand motion were converted to Snellen equivalents according to guidelines from a previous report.20

SD-OCT scans were performed for all patients enrolled using Spectralis OCT (Heidelberg Engineering, Vista, CA), which provides 40,000 A-scans per second with 7-µm optical and 3.5-µm digital axial resolution. For each patient, vertical SD-OCT scans through the fovea, which consisted of 512 A-scans per line, were obtained for both eyes. The thickness of each retinal layer was measured manually using the included Heidelberg Eye Explorer software (version 1.5.12.0; Heidelberg Engineering).

We classified retinal layers for thickness measurement (Fig. 2) as follows: nerve fiber layer (NFL), ganglion cell layer (GCL) + inner plexiform layer (IPL), inner nuclear layer (INL), OPL, outer nuclear layer (ONL), and PRL. Because we experienced considerable intra-observer variability when measuring the thickness of the GCL and IPL separately at the reattached retina, the thickness of the GCL+IPL was measured as a single unit in this study. The thicknesses of each retinal layer were measured at 2800 µm and 3000 µm from the foveal center in the superior and inferior directions, respectively (Fig. 3A). We defined regions of retinal thickness measurements as follows (Fig. 3B):

1. Reattached region: measuring points in the reattached retina located in the eye that received the retinal reattachment procedure (Fig. 3B, region [a]);
2. Unaffected region of the operated eye: measuring points in the undetached normal retina located in the eye that received the retinal reattachment procedure (Fig. 3B, region [b]); and
3. Corresponding region of the fellow eye: corresponding measuring points of the reattached region or unaffected region of the fellow eyes (Fig. 3B, region [a', b']).

A single observer (JHK), who was masked as to whether the eye had superior half or inferior half retinal detachment, performed the measurements, and the mean value of thickness measured at 2800 µm and 3000 µm was used for analysis. Comparisons of the thickness of each retinal layer were performed according to the following categories:

1. Comparison within eyes receiving retinal reattachment surgery: comparison between the reattached region and the unaffected region of the operated eye; and
2. Comparison within the fellow eyes: comparison between the corresponding region of the reattached region and the corresponding region of the unaffected region.

Correlation analysis was performed for retinal layers showing significant differences in thickness between the reattached region and the unaffected region of the operated eye. Correlations between the difference in thickness of retinal layers and both the duration of retinal detachment and duration between the retinal reattachment procedure and SD-OCT scan were evaluated. In addition, correlations between the difference in thickness of retinal layers and postoperative visual acuity and difference in pre-operative and postoperative best corrected visual acuity (BCVA, logarithm of the minimum angle of resolution units) were evaluated in eyes with fovea involving or splitting RRD. Eyes were divided into two groups, those who had scleral buckling procedure and those who underwent PPV. The duration of retinal detachment, the duration between surgery and SD-OCT scan, and difference in the thickness of retinal layers showing significant differences in thickness...
TABLE 1. Patient’s Characteristic

<table>
<thead>
<tr>
<th>Retinal Layers</th>
<th>Age, mean ± SD, y (range)</th>
<th>Sex, N</th>
<th>SE of fellow eyes, mean ± SD, D (range)</th>
<th>Visual acuity, mean ± SD, logMAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48.8 ± 13.4 (21–69)</td>
<td>Male</td>
<td>−1.87 ± 2.05 (−5.50–1.13)</td>
<td>Pre-operative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td>0.79 ± 0.82</td>
</tr>
<tr>
<td>Location of retinal detachment, N</td>
<td></td>
<td>Superior half</td>
<td>16</td>
<td>Postoperative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior half</td>
<td>12</td>
<td>0.30 ± 0.40</td>
</tr>
<tr>
<td>Extent of retinal detachment, N</td>
<td></td>
<td>1/4 quadrant or less</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/4 to 1/2 quadrant</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than 1/2 quadrant</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Types of surgery, N</td>
<td></td>
<td>Scleral buckling</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPV</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPV + scleral buckling</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Duration between surgery and OCT scan, mean ± SD, mo (range)</td>
<td></td>
<td>10.4 ± 6.9 (6–29)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; SE, spherical equivalent; logMAR, logarithm of the minimum angle of resolution; PPV, pars plana vitrectomy; OCT, optical coherence tomography.

RESULTS

Twenty-eight patients were enrolled in the result analyses. The mean (± SD) duration of retinal detachment was 6.9 ± 3.9 days (range 2–14 days). The mean spherical equivalent refractive error of the fellow eyes was −1.87 ± 2.03 D (range −5.5–1.13 D). The fovea was detached in 16 eyes, split in three eyes, and spared in nine eyes. Fourteen eyes received a scleral buckling procedure, 12 eyes received PPV, and two eyes received a combined PPV and scleral buckling procedure. Clinical characteristics of the patients are shown in Table 1. All surgeries were successfully performed without any intraoperative or postoperative complications, and delayed subretinal fluid absorption on binocular funduscopic examination was not noted. The SD-OCT images showed complete resolution of subretinal fluid except for small localized subfoveal fluid blebs noted in three eyes. The pre-operative

DISCUSSION

In this study, we attempted to evaluate changes in retinal microstructure following retinal detachment by measuring the

TABLE 2. Comparison of Thickness of the Retinal Layer between the Reattached Region and the Unaffected Region in the Operated Eye

<table>
<thead>
<tr>
<th>Retinal Layers</th>
<th>Reattached Region (a)</th>
<th>Unaffected Region (b)</th>
<th>P Value*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFL</td>
<td>54.45 ± 6.88</td>
<td>52.54 ± 7.56</td>
<td>0.150</td>
<td>0.900</td>
</tr>
<tr>
<td>GCL+IPL</td>
<td>48.93 ± 6.86</td>
<td>47.88 ± 5.43</td>
<td>0.464</td>
<td>1.000</td>
</tr>
<tr>
<td>INL</td>
<td>22.89 ± 4.42</td>
<td>22.62 ± 4.64</td>
<td>0.722</td>
<td>1.000</td>
</tr>
<tr>
<td>OPL</td>
<td>23.13 ± 3.53</td>
<td>24.76 ± 4.29</td>
<td>0.070</td>
<td>0.420</td>
</tr>
<tr>
<td>ONL</td>
<td>39.64 ± 10.00</td>
<td>47.07 ± 7.18</td>
<td>0.002</td>
<td>0.012</td>
</tr>
<tr>
<td>PRL</td>
<td>41.93 ± 5.84</td>
<td>45.69 ± 4.32</td>
<td>0.003</td>
<td>0.018</td>
</tr>
</tbody>
</table>

For location of (a) and (b), refer to Figure 3.

BCVA were 0.79 ± 0.82, which improved to 0.30 ± 0.40 at the final visit. The mean duration between the surgery and SD-OCT scan was 10.4 ± 6.9 months (range 6–29 months).

When compared within eyes receiving retinal reattachment surgery, the thicknesses of ONL and PRL in the reattached region were significantly thinner than the unaffected region of the operated eye (Table 2; $P = 0.002$, $P = 0.005$). The differences in the thicknesses of ONL and PRL between the reattached region and the unaffected region of the operated eye were statistically significant after Bonferroni’s correction (Table 2; $P = 0.012$, $P = 0.018$). The mean thicknesses of ONL and PRL in the reattached region were 39.64 ± 10.00 μm and 41.93 ± 5.84 μm, respectively, whereas the mean thicknesses of these layers in the unaffected region of the operated eye were 47.07 ± 7.18 μm and 45.69 ± 4.32 μm, respectively. The relationships between the duration of retinal detachment and differences in thicknesses of ONL and PRL were not significant (Fig. 4; $P = 0.746$, $P = 0.521$). Also, the relationship between the duration between retinal reattachment procedure and SD-OCT scan and the difference in thickness of ONL and PRL was not significant (Fig. 5; $P = 0.575$, $P = 0.486$). When the 19 eyes with fovea involving/splitting RRD were analyzed, the difference in pre-operative and postoperative logMAR visual acuity was significantly correlated with the difference in the thickness of ONL ($P = 0.016$, $r = −0.55$). However, the relationship between the difference in visual acuity and the difference in thickness of PRL ($P = 0.076$), and between postoperative visual acuity, and the differences in ONL ($P = 0.165$) and PRL ($P = 0.258$) were not significant.

In comparisons between the corresponding locations of the reattached region and the corresponding locations of the unaffected region, however, we did not appreciate any significant differences in thicknesses of each retinal layer (Table 3).

When divided into two groups according to the types of surgery, the duration of retinal detachment and the duration between surgery and SD-OCT scan was not different between the two groups ($P = 0.856$ and $P = 0.852$, respectively). The difference in the thickness of ONL was 8.41 ± 11.21 μm and 5.77 ± 12.89 μm in eyes that underwent scleral buckling (N = 14) and eyes that underwent PPV (N = 12), respectively. The difference was not significant ($P = 0.585$). The difference in the thickness of PRL was 5.32 ± 6.99 μm and 1.82 ± 4.58 μm in eyes that underwent scleral buckling and eyes that underwent PPV, respectively. The difference was not significant ($P = 0.209$).

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thicknesses of retinal layers based on SD-OCT images. We revealed significant thinning of ONL and PRL in reattached retina, although the mean duration of retinal detachment in our patients was less than 1 week. To our knowledge, based on a computerized MEDLINE search for similar reports, this is the first study designed to quantify differences in thicknesses of each retinal layers between reattached retina and normal retina based on SD-OCT images.

Although there are close correspondences between OCT signals and histologic findings, there is a degree of mismatch that occurs when superimposing histologic and OCT images due to tissue shrinkage during histologic processing. Thus, we believe that thicknesses presented in our study based on in vivo OCT image may more accurately represent real thicknesses of biologic tissue. Our study differs from previous studies of human material in several other ways. One study investigated human reattached retina following approximately 3.5 weeks of retinal detachment and revealed atrophy of the photoreceptors, outer ONL, and OPL. In that study, however, the average duration of retinal detachment was relatively long compared with our study, the control region was just the ‘normal undetached retina’, rather than an appropriate corresponding region, and atrophy was not verified by statistical analysis.

The results of our study demonstrate limited recovery of retinal thickness despite the short duration of retinal detachment, and the greater than 6 month reattachment period in all cases. Experimental retinal detachment models have shown degenerations of retinal layers following acute retinal detachment. However, the follow up periods after retinal reattachment were limited to no longer than 4 months in most animal experiments, so the long term recovery of reattached retina has not yet been fully revealed. Previous studies with 5 to 6 month follow up periods after retinal reattachment, showed gradual lengthening of the photoreceptor outer segment in animals with a 7 day or less detachment period. The length of photoreceptor outer segment was almost normalized at the end of the follow up period in these studies. However, significant thinning of ONL and PRL was observed in our study even after a follow up period of 6 months or longer.

In animal experiments, retinal degeneration tends to worsen as the detachment period increases. In this study, however, we could not demonstrate that differences in the thicknesses of ONL and PRL were correlated with duration of retinal detachment among eyes with less than 2 weeks of symptoms. More specifically, notable additional decreases in

![Figure 4](https://iovs.arvojournals.org/doi/abs/10.1167/iovs.12-10904)  Difference in thickness of outer nuclear layer (A) and photoreceptor layer (B) between the re-attached region and unaffected region of the operated eye, according to the duration of retinal detachment.

![Figure 5](https://iovs.arvojournals.org/doi/abs/10.1167/iovs.12-10904)  Difference in thickness of the outer nuclear layer (A) and photoreceptor layer (B) between the re-attached region and unaffected region of the operated eye, according to the period between retinal reattachment surgery and time spectral-domain optical coherence tomography scan was performed.

### Table 3. Comparison of Retinal Layer Thickness in the Fellow Eye between Corresponding Regions of the Reattached Region and Corresponding Regions of the Unaffected Region

<table>
<thead>
<tr>
<th>Retinal Layers</th>
<th>Corresponding Region (a’) of Reattached Region</th>
<th>Corresponding Region (b’) of Unaffected Region</th>
<th>P Value*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFL</td>
<td>52.39 ± 5.97</td>
<td>51.57 ± 5.42</td>
<td>0.357</td>
<td>1.000</td>
</tr>
<tr>
<td>GCL+IPL</td>
<td>47.28 ± 7.02</td>
<td>45.73 ± 4.47</td>
<td>0.368</td>
<td>1.000</td>
</tr>
<tr>
<td>ONL</td>
<td>20.50 ± 4.40</td>
<td>21.55 ± 3.75</td>
<td>0.248</td>
<td>1.000</td>
</tr>
<tr>
<td>OPL</td>
<td>23.97 ± 3.17</td>
<td>23.67 ± 3.30</td>
<td>0.723</td>
<td>1.000</td>
</tr>
<tr>
<td>ONL</td>
<td>46.07 ± 5.29</td>
<td>45.74 ± 6.46</td>
<td>0.768</td>
<td>1.000</td>
</tr>
<tr>
<td>PRL</td>
<td>45.97 ± 2.85</td>
<td>44.62 ± 3.44</td>
<td>0.095</td>
<td>0.570</td>
</tr>
</tbody>
</table>

* Paired t test.
† Paired t test with Bonferroni’s correction.
thickness of ONL and PRL were not observed in eyes with a little longer detachment period in our study. Our results indirectly support recent reports indicating that within the first week, the duration of macular detachment does not influence postoperative acuity.25–27 However, care should be taken in interpreting the result of the present study and previous studies.25–27 It should be emphasized that, once detached, there was ONL and PRL thinning in the area of detached retina irrespective of the promptness to reattachment. Given this, the structural changes found in our study may highlight the importance of initial injury to the retinal tissue, such as apoptosis,28,29 on the long term structural prognosis. Structural integrity of the PRL is closely associated with visual function. Considering the results of a previous study that demonstrated a positive correlation between ONL cell counts and contrast gains of electroretinography,3 the structural integrity of the ONL is thought to be associated with visual function. How can we translate our observation into clinical practice? Once the macula is detached, it is likely that little delay may not have significant influence on the visual prognosis. However, the more important point is that early intervention is needed prior to macular detachment because long term structural sequelae may remain despite only few days of detachment duration. More controlled studies involving larger number of cases may more accurately reveal the influence of retinal detachment duration on the retinal microstructure and the efficacy of early intervention after macular involvement.

In this study, overall decreases in the thicknesses of outer retinal layers, including ONL, OPL, and PRL were observed in the reattached retina, whereas thicknesses of the inner retinal layers were not affected. This result agrees with those of a previous study using a murine model, which showed that the thicknesses of outer retinal structures significantly decreased after detachment over time, whereas the thickness of the inner retina did not significantly change according to either histology or SD-OCT in mice.24 Another study showed similar results for human material.12

In this study, we found a significant correlation between changes in visual acuity and the difference in thickness of the ONL in patients with fovea involving/splitting RRD; this finding may suggest an important role of ONL integrity on visual acuity. Further studies investigating subfoveal ONL will be required to address this hypothesis.

Several previous studies showed that retinal thickness is closely related to both axial length30–32 and spherical equivalent.31,32 Because information about the precise preoperative axial lengths and spherical equivalents of eyes that have undergone retinal reattachment procedure is limited, comparisons between the regions within the same eye were performed to avoid the influence of these factors. However, it is also well known that there are topographic differences in retinal thickness in normal eyes.30,31 It is possible that this natural difference in thickness may influence the results of comparisons between reattached and the opposite regions because 16 patients had superior half retinal detachment, whereas only 12 patients had inferior half retinal detachment. Thus, we performed additional comparisons between the corresponding region of the reattached retina and the corresponding region of the unaffected retina to identify this influence. Although the thicknesses of each retinal layer were slightly different between the two regions, these differences were not statistically significant, suggesting that natural differences in retinal thickness do not affect the results of comparisons between the reattached versus the unaffected retina. Moreover, although the differences were not statistically significant, all the retinal layers except the INL were slightly thicker in the corresponding region of the reattached retina. It is possible that the original thickness of the reattached region was slightly greater than that of the unaffected region in some eyes, thus, leading to an underestimation of the amount of decrease in thickness of the reattached region. Thus, the significant thinning of ONL and PRL observed in the reattached region in this study support our conclusion, despite the possibility of underestimation described above.

There are several limitations of this study: First, the study sample was small, probably because we restricted the inclusion criteria to patients with only half retinal detachment. Second, the periods between the retinal reattachment surgery and SD-OCT scans varied. In particular, this period was 8 months or less in 20 of 28 eyes. It is possible that the significant differences in thickness found in our study were partially caused by insufficient time for recovery. It is also possible that varying periods between retinal reattachment surgery and SD-OCT scans may have an influence on the results of the correlation analyses, including the correlation between the difference in thickness of retinal layers and both the duration of retinal detachment and visual acuity. Further, prospective studies with same periods between surgery and SD-OCT scans for each case may provide more robust data. Third, all of the patients in our study underwent a retinal reattachment procedure within 2 weeks after onset of visual symptoms. Thus, the results of correlation analyses between the duration of retinal detachment and the difference in thickness of retinal layers may be valid for patients with a relatively short duration of retinal detachment. Forth, the determination of the duration of retinal detachment was dependent on the reliability and precision of each patient’s memory.

In summary, we found significant thinning of ONL and PRL in reattached retina in patients with relatively short durations of retinal detachment and periods of reattachment 6 months or more using in vivo SD-OCT images. We hope that further studies will more clearly reveal abnormalities in retinal microstructure and elucidate their clinical significance in reattached retina.

Acknowledgments

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