Macular Migration toward the Optic Disc after Inner Limiting Membrane Peeling for Diabetic Macular Edema

Munemitsu Yoshikawa, Tomoaki Murakami, Kazuaki Nishijima, Akihito Uji, Ken Ogino, Takahiro Horii, and Nagabisa Yoshimura

PURPOSE. To investigate the papillofoveal distance and its association with retinal thickness on optical coherence tomography (OCT) images after vitrectomy for diabetic macular edema (DME).

METHODS. In this retrospective case series, 72 eyes of 57 consecutive patients who underwent vitrectomy for DME were included. Retinal images dissecting the fovea horizontally were obtained using OCT before and after vitrectomy. After identification of the disc margin and the presumed foveal center, the papillofoveal distance was measured on the OCT images. The association of the distance with retinal thickness and peeling of the inner limiting membrane (ILM) was evaluated.

RESULTS. The papillofoveal distance was significantly shorter after vitrectomy (3956.1 ± 299.0 µm vs. 3759.6 ± 331.3 µm; P < 0.001), and the shortening was correlated negatively with the total and inner retinal thickness in the temporal subfield (r = −0.29, P = 0.012 and r = −0.34, P = 0.004, respectively). Shortening of the papillofoveal distance was greater in 54 eyes in which ILM peeling was performed compared with 18 eyes in which ILM peeling was not performed (254.7 ± 159.3 µm vs. −9.7 ± 83.5 µm; P < 0.001). No differences were seen in the papillofoveal distance and retinal thickness before and after surgery between eyes with and without preoperative epiretinal membrane or posterior vitreous detachment. The total and inner thicknesses in the temporal subfield were thinner in eyes that underwent ILM peeling than those without ILM peeling (P < 0.001 and P < 0.001).

CONCLUSIONS. The papillofoveal distance on OCT images was shortened and the retina in the temporal subfield was thinned in eyes that underwent ILM peeling to treat DME. (Invest Ophthalmol Vis Sci. 2013;54:629–635) DOI:10.1167/iovs.12-10907

At the incipient fovea, the cones move centripetally, whereas the inner cells including the bipolar cells, ganglion cells, and Müller cells are displaced centrifugally, which results in the cones becoming condensed and packed on the fovea and an array of radiating Müller cells and bipolar cells. After maturation, the physiologic fovea seems static, although mechanical forces in the pathologic vitreo-retinal interface often change the macular morphology in eyes with an epiretinal membrane (ERM) and macular hole. In addition, the pathophysiology, including the vascular hyperpermeability and ischemia associated with retinal vascular diseases, results in thickening of the retinal parenchyma or macular edema. However, it remains to be determined how the retinal components affect the macular morphologies in the individual diseases.

The inner limiting membrane (ILM) is a basement membrane to which the endfoot of the Müller cells are attached. This innermost retinal structure, comprised of type IV collagen fibers, glycosaminoglycans, laminin, and fibronectin, is rigid and provides the scaffold for the mesenchymal cells, possibly leading to macular pathologies. It seems that enlargement of the axial length of the globe disproportionate to the static ILM could result in pathologic thickening of the retinal parenchyma including retinoschisis and retinal detachment in eyes with high myopia. ILM peeling to treat macular holes increases the success rate of hole closure, suggesting that the ILM contributes to the pathogenesis. In addition, removing the ILM, which is a scaffold for the proliferative tissue in the vitreoretinal interface, reduces the risk of development of macular pucker postoperatively.

Diabetic macular edema (DME) is a leading cause of severe visual loss in patients with diabetic retinopathy (DR). In addition to medical therapeutic strategies, pars plana vitrectomy (PPV) can eliminate several pathologic changes that contribute to thickening of the retinal parenchyma and neuroglial dysfunction in the macula. PPV is the only treatment that eliminates mechanical traction caused by the posterior hyaloid membrane or the ERM and improves the pathophysiologic conditions, retinal oxygenation, and reduced vascular permeability by removing the vitreous that contains growth factors from the ischemic retina and cytokines that modulate the inflammatory responses. Despite numerous studies that have described ILM peeling for DME, it is controversial whether or how ILM peeling combined with PPV affects visual function and macular morphologies in DME.

The current study investigated the macular morphologies after PPV and, for the first time, reported shortening of the papillofoveal distance and decreased retinal thickness in the temporal subfield in eyes with ILM peeling for DME.

METHODS

Patients

We retrospectively reviewed 72 consecutive eyes of 57 patients (mean age, 65.7 ± 7.2 years), after the exclusion of three eyes with poor-quality optical coherence tomography (OCT) images. Eleven eyes had...
moderate nonproliferative diabetic retinopathy (NPDR), 40 eyes severe NPDR, and 21 eyes PDR. These patients underwent PPV for clinically significant macular edema at the Department of Ophthalmology in Kyoto University Hospital between November 2007 and September 2011, and were followed for more than 6 months. A posterior vitreous detachment (PVD) was observed in 8 eyes and an ERM involving the fovea was present in 17 eyes at baseline. All investigations adhered to the tenets of the Declaration of Helsinki. The institutional review board and ethics committee of Kyoto University Graduate School of Medicine approved the study.

### Intervention

A standard PPV was performed.20 After insertion of a 23-gauge cannula and core vitrectomy, the posterior hyaloid membrane or ERM was peeled if present21 and, subsequently, the ILM in the macula was peeled using ILM forceps in 54 eyes following visualization with indocyanine green staining. Cataract surgery (phacoemulsification, aspiration, and intraocular lens implantation) was performed in 48 eyes. A peribulbar injection of triamcinolone (Kenakolt-A; Bristol Pharmaceuticals KK, Tokyo, Japan) was administered at the end of surgery to 25 eyes.

### Optical Coherence Tomography

Retinal sectional images were acquired using OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), and horizontal images in the cross-hair mode (30°) centered on the fovea were evaluated at baseline and 6 months after PPV. We first identified the presumed foveal center as described previously.22 Briefly, the inner retinal layers from the nerve fiber layer (NFL) to Henle’s layer were observed in the periphery and, when traced to the fovea, these layers disappeared. We determined the center point of this area as the presumed foveal center. We further identified the edge of the retinal pigment epithelium (RPE) (or edge of the sclera in eyes with peripapillary atrophy) as the disc margin. We then manually measured the distance from the disc margin to the presumed foveal center and this was defined as the papillofoveal distance.

We also identified the point 1 mm from the presumed foveal center in the nasal or temporal subfield, which could be considered representative of each subfield of the Early Treatment Diabetic Retinopathy Study parafoveal ring and measured the distances from the innermost retina (ILM or NFL after ILM peeling) to the outer border of the INL as the inner thickness and from the inner border of the outer plexiform layer to the RPE as the outer thickness at each point. All measurements were made in a masked fashion. We evaluated the changes in papillofoveal distance and its association with retinal thickness. We further investigated the effects of preoperative ERM or posterior hyaloid membrane or ILM peeling on the macular morphology.

### Statistical Analysis

The results are expressed as the means ± SD. The Student's t-test was used to compare quantitative data populations with normal distributions and equal variance. The data were analyzed using the Mann-Whitney U test for populations with nonnormal distributions or unequal variance. Significant differences in the sampling distributions were determined using Fisher's exact test. Linear regression analysis was performed to test the statistical correlation with commercial software (PASW Statistics, version 18; SPSS, Inc., Chicago, IL). *P* < 0.05 was considered significant.

### RESULTS

In the current study, we measured the papillofoveal distance on OCT images in all 72 eyes and found that the distance was significantly shorter 6 months after PPV (3956.1 ± 299.0 μm vs. 3759.6 ± 331.3 μm; *P* < 0.001) (Table 1). The retinal thicknesses in the central, nasal, and temporal subfields also decreased, which agrees with previous studies.14,21,23,24 (Table 1). We then investigated the relationship between the horizontal and vertical macular changes after PPV and showed that shortening of the papillofoveal distance was associated negatively with the total or inner thicknesses in the temporal subfield after PPV (*r* = −0.29, *P* = 0.012 and *r* = −0.34, *P* = 0.004, respectively) compared with no association between the shortening and the central thickness (Table 2). We also found that the shortening tended to be correlated positively with the total or outer thicknesses in the nasal subfield, although the correlations did not reach significance (Table 2).

### Table 2. Association between Shortening of the Papillofoveal Distance and Retinal Thicknesses after PPV for DME

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation with Shortening of Papillofoveal Distance</th>
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<tr>
<td>Center point thickness</td>
<td><em>r</em> = −0.02, <em>P</em> = 0.866</td>
</tr>
<tr>
<td>Total thickness of the nasal subfield</td>
<td><em>r</em> = 0.23, <em>P</em> = 0.054</td>
</tr>
<tr>
<td>Inner thickness of the nasal subfield</td>
<td><em>r</em> = −0.21, <em>P</em> = 0.770</td>
</tr>
<tr>
<td>Outer thickness of the nasal subfield</td>
<td><em>r</em> = 0.25, <em>P</em> = 0.051</td>
</tr>
<tr>
<td>Total thickness of the temporal subfield</td>
<td><em>r</em> = −0.29, <em>P</em> = 0.012</td>
</tr>
<tr>
<td>Inner thickness of the temporal subfield</td>
<td><em>r</em> = −0.34, <em>P</em> = 0.004</td>
</tr>
<tr>
<td>Outer thickness of the temporal subfield</td>
<td><em>r</em> = −0.11, <em>P</em> = 0.373</td>
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</table>
We thus investigated the relationship between the shortening of the papillofoveal distance and the presence of a preoperative ERM or PVD and intraoperative ILM peeling. Shortening of the papillofoveal distance was significantly greater in 54 eyes with ILM peeling than that in 18 eyes in which the ILM was not peeled (234.7 ± 159.3 µm vs. -9.7 ± 83.5 µm; P < 0.001) (Figs. 1–3; Tables 3, 4; see Supplementary Material and Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.12-10907/-/DCSupplemental); no differences were seen in the shortening in association with a preoperative ERM or the vitreous status (P = 0.782 and P = 0.221, respectively; see Supplementary Material and Supplementary Table S2, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.12-10907/-/DCSupplemental). This suggested that ILM peeling is a factor that affects the macular morphologies after PPV. Despite the significant differences in morphology, there were no differences in the course of the logarithm of the minimum angle of resolution (logMAR) between eyes with ILM peeling and those without ILM peeling.

When we compared the OCT parameters in eyes with ILM peeling to those in which ILM peeling was not performed, in addition to shortening of the papillofoveal distance, the total and inner thicknesses in the temporal subfield were significantly thinner in eyes with ILM peeling than in those in which ILM peeling was not performed; the outer thickness was almost the same in the two groups (Table 3). We did not find significant differences in the thicknesses of the central and nasal subfields between eyes with and without ILM peeling (Table 3). Evaluation of the qualitative findings indicated that a depression of inner retinal surface in the temporal area occurred in 19 (35.2%) of 54 eyes with ILM peeling (Fig. 4), although there was no depression in 18 eyes without ILM peeling (P = 0.020).

**DISCUSSION**

There are several publications documenting that PPV results in decreased macular thickness. However, despite publication of many studies on ILM peeling for DME, the effect of ILM peeling on the macular morphology after PPV remains ill-defined. In the current study, we showed for the first time that shortening of the papillofoveal distance is associated with a decrease in retinal thickness in the temporal subfield. Eyes in which the ILM was peeled had a shorter papillofoveal distance than those in which ILM peeling was not performed, suggesting that the rigid preoperative ILM counteracted unrecognized biomechanical forces, which were seen after ILM removal, and displaced the fovea toward the optic disc.

We considered that shortening of the papillofoveal distance after PPV might depend on either factors such as removal of mechanical forces at baseline or the release of inherent forces in the retina where ILM was peeled. Macular dragging in retinopathy of prematurity (ROP) or familial exudative vitreoretinopathy (FEVR) often show the macular displacement to the temporal side according to the contraction by proliferative tissues and so on. In this study,
mechanical forces by ERM or posterior hyaloid membrane modify the baseline macular morphology and the compression caused by unbalanced edema could displace the fovea. The removal of these pathologic forces might facilitate return of the fovea to the correct position. However, preoperative ERM and PVD did not have effects on the shortening of the papillofoveal distance in our study. It supports the inherent forces in the retina, although the random orientation of the tractional forces might hide the statistical significance of the foveal displacement. Compared with these factors, ILM peeling caused significant shortening of the papillofoveal distance, whereas we did not observe the changes in the papillofoveal distance in eyes in which ILM peeling was not performed. The ILM is a rigid basement membrane that contributes to less retinal elasticity. No studies have described the contractile properties of the ILM per se compared with Bruch’s membrane with elastic fibers. Therefore, we speculated that the release of unknown forces in the retinal parenchyma might be the major cause of shifting the fovea nasally after ILM peeling.

We demonstrated that the shorter the papillofoveal distance got after surgery, the smaller the retinal thickness in the temporal subfield became. We speculated that foveal displacement toward the optic disc leads to stretching and the thinning of the retinal parenchyma in the temporal subfield. Inversely, the thinning might represent degenerative or atrophic changes, resulting in an imbalance of the biomechanical forces between the nasal and temporal subfields and concomitant foveal migration. We further found that the retina was thinner in eyes treated with ILM peeling compared with those that did not and that a sharp depression of the inner surface in the temporal subfield was seen in 19 eyes (35.2%) in which ILM peeling was performed compared with those in which it was not, which agrees with both possible explanations. Contrary to the temporal subfield, the shortening of the papillofoveal distance was correlated positively with the postoperative retinal thickness in the nasal subfield, but not significantly. However, there were no differences in the retinal thickness change in the nasal subfield between eyes with and without ILM peeling. These data suggested that after ILM peeling foveal displacement might increase the retinal thickness in the nasal subfield, which was counteracted by both the improvement of edematous changes and the degenerative or atrophic changes in the same subfield. However, we did not completely exclude the possibility of surgical artifact by ILM peeling. Further, it remains to be investigated whether such macular deformation occurs in other diseases treated by ILM peeling or after other interventions for macular edema.

The findings after the ILM removal included slight retinal whitening in the acute phase, dissociation of the optic NFL in the subacute phase, and thinning of the temporal retina in the chronic phase. In the current study, we documented for the first time shortening of the papillofoveal distance after ILM peeling for DME. Since the ILM is a basement membrane without contractile properties, we speculated that the dynamic changes in the macular morphology after ILM peeling might.
depend on retinal components other than the ILM, such as axon contractility in the NFL and asymmetry of the biomechanical forces by cellular components after DME resolution. Nerve fibers are comprised mainly of microtubules and actin filaments, and the contractile properties by an actomyosin interaction might result in the macular migration. Another possibility is the zigzag course of the NFL after ILM peeling. A recent publication using en face OCT images reported concentric dark macular spots in the NFL after ILM peeling, suggesting that the nerve fibers might run a zigzag course and concomitantly produce the contractile forces toward the optic disc. A third possibility is the asymmetry of the biomechanical forces by cellular components after DME resolution. The capillaries around the fovea are displaced toward the optic disc after PPV, whereas the major vessels and photocoagulation scar are static. (E) A preoperative sectional image dissecting the green arrow in (D) shows foveal cystoid spaces with a papillofoveal distance of 4061 μm (red arrow). (F, G) The papillofoveal distance decreased to 3785 μm after PPV.

Table 3. Postoperative OCT Parameters in Eyes with and without ILM Peeling

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ILM Peeling (+) (54 Eyes), μm</th>
<th>ILM Peeling (-) (18 Eyes), μm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillofoveal distance</td>
<td>3713.7 ± 295.8</td>
<td>3985.5 ± 283.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Center point thickness</td>
<td>304.7 ± 192.5</td>
<td>313.8 ± 156.0</td>
<td>0.884</td>
</tr>
<tr>
<td>Total thickness of the nasal subfield</td>
<td>418.1 ± 92.3</td>
<td>391.6 ± 80.0</td>
<td>0.280</td>
</tr>
<tr>
<td>Inner thickness of the nasal subfield</td>
<td>220.8 ± 51.1</td>
<td>210.7 ± 63.4</td>
<td>0.497</td>
</tr>
<tr>
<td>Outer thickness of the nasal subfield</td>
<td>197.4 ± 57.7</td>
<td>172.6 ± 29.2</td>
<td>0.085</td>
</tr>
<tr>
<td>Total thickness of the temporal subfield</td>
<td>287.7 ± 77.7</td>
<td>381.2 ± 123.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inner thickness of the temporal subfield</td>
<td>151.5 ± 49.4</td>
<td>213.6 ± 90.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outer thickness of the temporal subfield</td>
<td>136.2 ± 50.3</td>
<td>155.5 ± 64.3</td>
<td>0.194</td>
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</table>
forces caused by cellular components in the macula. Neuroglial dysfunction in the temporal subfield, which is often vulnerable to ischemic changes in patients with DR, might result in contractile forces in the nasal subfield superior to those in the temporal subfield. We hypothesized that biomechanical asymmetry was counteracted by ILM rigidity, until the PPV combined with ILM peeling resulted in a foveal shift toward the optic disc.

In conclusion, we showed for the first time that the fovea migrates toward the optic disc after ILM peeling for DME, suggesting that the ILM might tether the retinal parenchyma and that the retinal parenchyma per se has contractile properties after ILM peeling.

References


