Progressive Changes of Regional Macular Thickness After Macular Hole Surgery With Internal Limiting Membrane Peeling

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Purpose. To determine the changes of regional macular thickness after successful macular hole surgery (MHS) with internal limiting membrane (ILM) peeling during a 24-month follow-up period.

Methods. In a prospective, interventional case study, the authors evaluated 24 eyes of 24 patients who underwent 23-gauge transconjunctival pars plana vitrectomy with triamcinolone-assisted ILM peeling to treat idiopathic macular hole. Examinations were performed before and 1, 2, 3, 6, 9, 12, and 24 months after surgery. Average regional macular thicknesses in the Early Treatment Diabetic Retinopathy Study sectors were measured by spectral-domain optical coherence tomography.

Results. The four inner sectors showed a significant reduction in the average retinal thickness at 1 month after surgery ($P \leq 0.0001$–0.020), and the thickness continued to decrease for 24 months except in the nasal sector. The four outer sectors had a significant increase at postoperative 1 month ($P = 0.0003$–0.029) and then progressively decreased during the postoperative 24 months. The postoperative regional macular thinning was statistically significant even between 12 and 24 months ($P = 0.0007$–0.026) in all sectors except in the inner nasal sector ($P = 0.13$). The postoperative percent reduction rate was significantly different among four inner sectors after postoperative 3 months ($P = 0.0029$–0.039) in the order of temporal > superior > inferior > nasal sectors.

Conclusions. These results suggest that a progressive macular thinning occurs for at least 2 years with different patterns of the changes in the macular regions after successful MHS with ILM peeling.

Keywords: macular hole, internal limiting membrane, retinal thickness, spectral-domain optical coherence tomography

Internal limiting membrane (ILM) peeling has become a common procedure during macular hole surgery (MHS).[1] ILM peeling increases the closure rate and lowers the reopening rate.[2–7] Regardless of these beneficial effects, ILM peeling has also been shown to lead to damage to the Müller cells,[8,9] because the ILM is the basement membrane of the Müller cells. In addition, ILM peeling has been reported to delay the recovery of the b-waves of the focal macular electroretinograms[10]; to lead to the development of arcuate striae appearance, which run in the direction of the optic nerve fibers on ophthalmoscopy and optical coherence tomography (OCT)[11–21]; and to cause a thinning or thickening of the macular retinal thickness.[22–24] However, it remains unknown whether these effects of ILM peeling are transient or progressive.

Spectral-domain OCT (SD-OCT) can obtain 3-dimensional images of the macula. The Cirrus high definition optical coherence tomography (HD-OCT; Carl Zeiss Meditec, Dublin, CA) automatically detects the position of the foveal center in the 3-dimensional macular scans (macular cube scan). It then adjusts the detected foveal center to be centered on the central subfield of the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. This function allows the examiner to measure the same area of the macula at the follow-up examinations.

The purpose of this study was to determine whether the changes in the thickness of the macula after successful MHS with ILM peeling are transient or progressive. To accomplish this, we followed 24 eyes of 24 patients for at least 24 months after the MHS. We used HD-OCT to determine the regional retinal thickness in the macular area.

Methods

We prospectively enrolled 27 eyes of 27 consecutive patients who had undergone MHS at Shinjo Ganka Institute, Miyazaki, Japan, and Nishigaki Ganka, Nagoya, Japan, between June 2008 and June 2010. The inclusion criteria were as follows: (1) presence of an idiopathic macular hole; (2) successful anatomical closure of the macular hole after 23-gauge transconjunctival three-port pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling; and (3) met all scheduled visits after the MHS. Eyes were excluded if they had myopia greater than 6 diopters, required a reoperation for postoperative complications, such as a reopening of the macular hole or a retinal detachment, a history of prior vitreoretinal surgery, poor OCT images (signal strength < 7), and a history of ocular surgeries. In addition, eyes were excluded if the patient had any ocular or systemic disorder that could affect the retinal thickness (e.g., glaucoma, optic nerve diseases, epiretinal membrane, age-related macular degeneration, or diabetes mellitus).

All of the patients had a comprehensive ophthalmological examination, including measurements of the refractive error, measurement of the best-corrected visual acuity (BCVA) with a Landolt chart (Richmond Products, Albuquerque, NM) at 5 m, slit-lamp examination, measurement of the IOP with a Goldmann applanation tonometer (Haag-Streit AG, Koeniz, Switzerland), dilated slit-lamp biomicroscopy with and without a contact lens, fundus photography, and HD-OCT examinations.

This study adhered to the tenets set forth in the Declaration of Helsinki. Approval for the data collection and analyses was obtained from the institutional review board of the Shinjo Ganka Institute and Nishigaki Ganka Hospital. A written informed consent was obtained from all of the patients for the surgery.

Patients were examined preoperatively, and after 1 day; 1 and 2 weeks; and 1, 2, 3, 6, 9, and 12 months postoperatively. Thereafter, the examinations were performed every 3 to 6 months.

All surgeries were performed by one surgeon (NO). All of the phakic patients underwent pars plana vitrectomy with phacoemulsification and placement of a posterior chamber intraocular lens to avoid a decrease in the postoperative BCVA because of a development of nuclear cataracts. After core vitrectomy, a posterior vitreous detachment was created by aspiration with a backflush needle in eyes that did not have posterior vitreous detachment. After the removal of the detached vitreous gel and the posterior hyaloid membrane, ILM peeling was performed using triamcinolone acetonide to make the ILM visible. The ILM peeling was begun by grasping the ILM over the superior macular region with forceps, and then the peeling was extended in a circumferential manner over the area, including the macula, without touching the retinal surface. The area involved the macula at a diameter of 6 mm (equivalent to the entire ETDRS sector area). Sulfur hexafluoride gas was used in all cases to tamponade the retina, and patients were instructed to maintain a prone position for 7 days.

We used the retinal thickness map analysis protocol of the Cirrus HD-OCT (Carl Zeiss Meditec). A macular cube scan of 200 $\times$ 200 pixels and five-line raster scan were performed at every visit by an experienced OCT examiner. The examiner discarded poor-quality images with a signal strength less than 7 and any scans with visible eye movements or blinking artifacts (discontinuous jump), poor centration, or incorrect segmentation.

The built-in software automatically calculated the average retinal thickness in each of the nine macular sectors in a 6-mm diameter circle centered on the fovea, as defined in the ETDRS.[25] The standard retinal sectors were the central and the superior, temporal, inferior, and nasal quadrants of the inner and outer rings. The diameter of the central ring was 1 mm, that of the inner ring was 3 mm, and that of the outer ring was 6 mm. We did not measure the retinal thickness in the central subfield before surgery because the central subfield includes a macular hole.

The change in the postoperative regional macular thickness was determined by subtracting the postoperative thickness from the preoperative thickness at each time. The rate of change of the average regional macular thickness was determined by dividing the difference between the preoperative thickness and postoperative thickness by the preoperative thickness at each time.

Numerical data were analyzed by paired and unpaired *t*-tests. The measured values for the four sectors in each ring were compared by ANOVA with post hoc comparisons by the Fisher's protected least significant difference test. A *P* less than 0.05 was accepted as statistically significant. The statistical analyses of the data were carried out with Statview 5.0 software (SAS Institute, Inc., Cary, NC).

Results

Subjects

We studied 27 eyes of 27 patients who were followed for at least 24 months. Three eyes were excluded because scheduled visits were not met. In the end, 24 eyes of 24 patients were analyzed with a mean follow-up period of 26.3 $\pm$ 4.6 months with a range of 24 to 36 months. The patients included 17 women (70.8%) and 7 men (29.2%), and their average age was 65.5 $\pm$ 6.4 years (mean $\pm$ SD) with a range from 47 to 77 years. The macular hole was successfully closed after the initial surgery in all of the eyes, and none had a reopening of the macula holes during the observational period. The preoperative decimal BCVA ranged from 0.02 to 0.70 (median, 0.15). The decimal BCVA at 24 months after surgery ranged from 0.1 to 1.5 (median, 1.0). The average BCVA in logarithm of the minimum angle of resolution (logMAR) improved over the 24-month follow-up period as shown in Supplementary Table S1. The postoperative logMAR BCVA was significantly better at 1 month than before surgery ($P < 0.0001$), and at 3, 6, and 12 months than at 1 month ($P =$ 0.0004, 0.0001, $<$0.0001, respectively). The BCVA at 12 and 24 months was significantly better than that at 3 months ($P =$ 0.0014 and 0.0057, respectively). The BCVA at 24 months was significantly better than that at 6 months ($P = 0.0066$). None of the eyes had a decrease in the BCVA by more than two lines during the 2-year postoperative follow-up period.

Temporal Changes of Regional Macular Thickness After Surgery

The temporal changes in the average regional macular thickness after MHS with ILM peeling had three different regional patterns (Fig. 1A, Supplementary Table S1). The thickness in the central subfield or fovea had a marked and significant reduction at 1 month after surgery ($P < 0.0001$), and then the thickness did not change significantly thereafter (Table). The four sectors of the inner ring also had a marked and significant reduction in retinal thickness at 1 month after surgery ($P <$ 0.0001–0.020), and the thicknesses continued to decrease until 24 months except the nasal sector (Fig. 1A, Table). The postoperative regional macular thinning was statistically significant between the thickness at 12 months and 24 months for the inner sectors except for the inner nasal sector ($P =$ 0.0007–0.026; Table).

In contrast to these two patterns, the thicknesses of the four sectors in the outer sectors were significantly increased at 1 month after surgery ($P =$ 0.0003–0.029), but then the thicknesses decreased continuously until 24 months (Fig. 1B, Table). The postoperative regional macular thinning was statistically significant even between the thickness at 12 months and 24 months for all of the outer sectors ($P =$ 0.0038–0.010; Table).

Comparisons of Postoperative Macular Thickness Changes of Sectors

To compare the changes of the regional macular thicknesses in the different sectors, the thicknesses at each postoperative

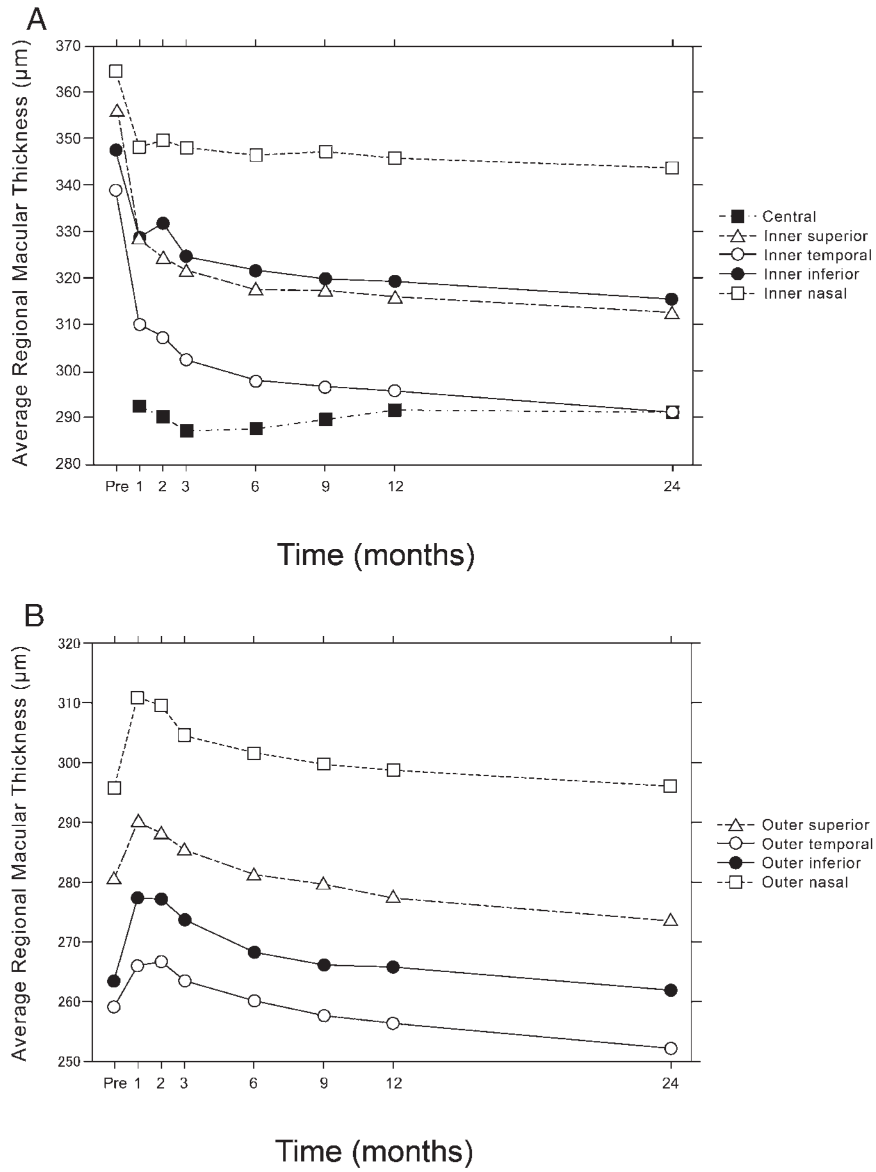

Figure 1. Temporal changes of average regional macular thickness after successful MHS with internal limiting membrane peeling. (**A**) Average foveal thickness and retinal thickness in the inner ring sectors. (**B**) Average retinal thickness in the outer ring sectors.

time were subtracted from the preoperative baseline thickness (Figs. 2A, 2B; Supplementary Tables S2, S3). Different chronological patterns were found for the four sectors in each of the inner and outer rings. The inner temporal, superior, and inferior sectors had significant progressive thinning with increasing time after the surgery. However, the inner nasal sector did not show a significant progressive thinning. The decrease in the thicknesses were significantly different for the four inner sectors at 9, 12, and 24 months after surgery ($P =$ 0.048, 0.042, and 0.029, respectively). The inner temporal and superior sectors showed significantly greater postoperative retinal thinning than the inner nasal sector at 9, 12, and 24 months after surgery ($P = 0.0063$–0.032).

All of the four sectors of the outer ring had an increase in the average thickness at 1 month after surgery and then had a progressive thinning to return to the preoperative baseline level. The outer temporal and superior sectors had similar postoperative thickness changes with time and both returned to preoperative baseline thickness at 6 months. They then became significantly thinner than the preoperative baseline level at 24 months ($P = 0.018$ and 0.026, respectively). In contrast, the thickness in the outer nasal and inferior sectors had similar postoperative thickness changes and then returned to the preoperative baseline thickness at 24 months. However, no significant differences were found among the four outer sectors at any time.

The preoperative baseline macular thickness differed in the four sectors ($P < 0.0001$); therefore, it was important to compare the rate of reduction of the postoperative average regional thicknesses in relation to the preoperative baseline thickness. The reduction rates in the regional thicknesses are shown in Supplementary Figures S1A, S1B and in Supplementary Tables S4, S5. The postoperative percent reduction rate was significantly different for the four inner sectors at 3, 6, 9, 12, and 24 months after surgery ($P =$ 0.039, 0.014, 0.0061, 0.0049, and 0.0029, respectively) in the order of temporal > superior > inferior > nasal sectors. The inner temporal sector had a significantly greater reduction rate than the inner nasal sector at 3 to 24 months ($P = 0.0004$–0.0078), and the inner inferior sector at 12 and 24 months ($P = 0.042$ and 0.037,

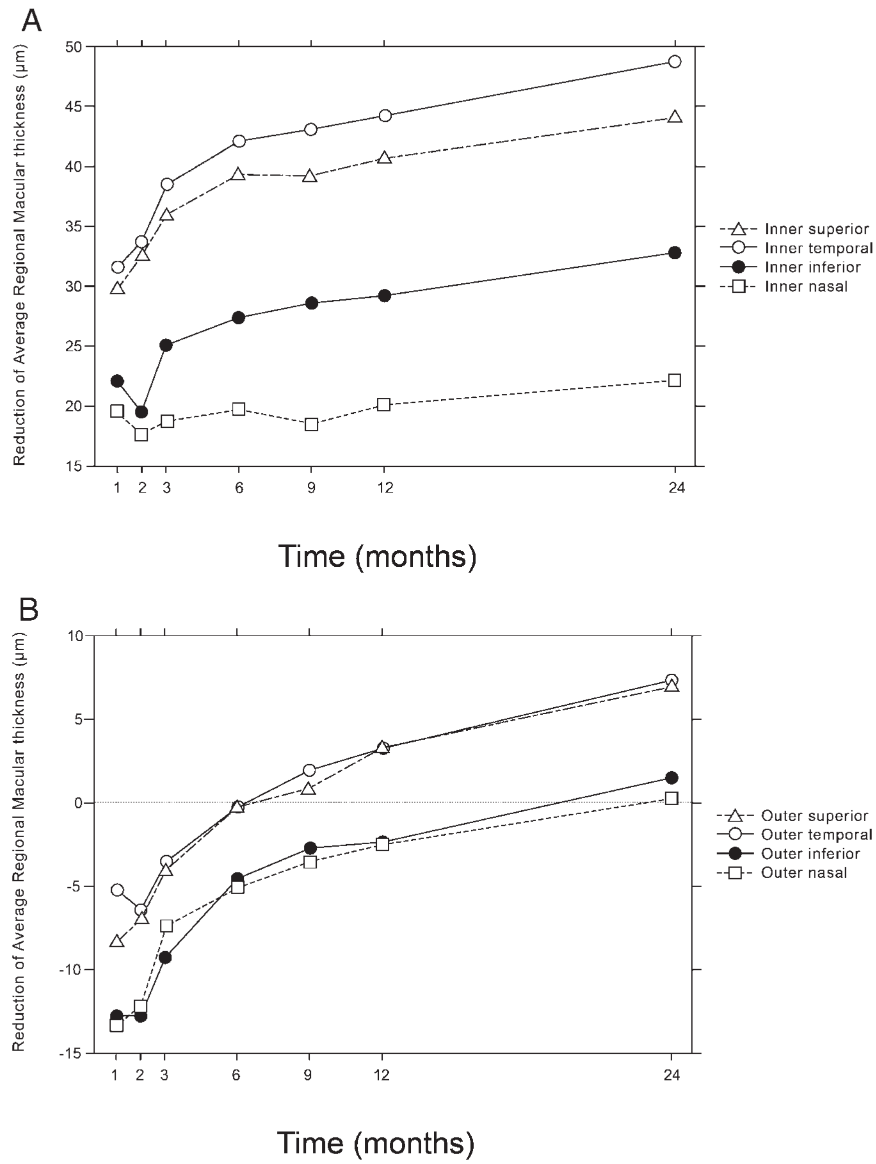

FIGURE 2. Temporal changes of differences of postoperative average regional macular thickness from preoperative baseline thickness after MHS. (**A**) Average retinal thickness in the inner ring sectors. (**B**) Average retinal thickness in the outer ring sectors.

respectively). The inner superior sector had a significantly greater reduction rate than the inner nasal sector at 3 to 24 months ($P = 0.008$–0.038). No significant differences were found for reduction rate of the postoperative average regional thickness among the four outer sectors at any time.

DISCUSSION

MHS with ILM peeling is associated with changes in the thickness of the macular area[22–24]; however, the question remains whether these retinal changes are transient or progressive. Our results showed that the average retinal thickness became progressively thinner for 2 years in the extrafoveal macular region even after a macular hole was closed after surgery with ILM peeling. This progressive thinning did not occur in the fovea after the macular hole closure. The progressive changes in the extrafoveal macula after successful MHS may be longer than previously believed.

The temporal changes of the average macular thickness were different for the inner and outer sectors. The macula in the inner sectors except the nasal sector had a progressive thinning for 24 months, whereas the outer sectors thickened with a peak at 1 month after surgery, and then gradually returned to the preoperative level in 6 to 24 months. However, the retina in the outer temporal and superior sectors became thinner than the baseline thickness, indicating that progressive retinal thinning occurred at least in these sectors. Thus, it is possible that both a recovery of the retinal thickening and thinning of the retina constitute the complicated temporal thickness changes of the outer sectors of the macular area.

It is unlikely that these temporal changes of the extrafoveal macular thickness after surgery are limited to the ETDRS sectors. Rather, our results suggest that the effects of MHS with ILM peeling on the macular area is related to the distance from the fovea. The opposite changes in the inner and outer sectors may be due to the anatomical characteristics of the retinal layers. The thickness of the retinal nerve fiber layer (RNFL) increases as a function of distance from the foveal center

Table. Statistical Comparison of Average Regional Macular Thickness Between Preoperative and Postoperative Time Points

Sectors	Pre vs. 1 month	1 month vs. 2 months	1 month vs. 3 months	1 month vs. 6 months	1 month vs. 12 months	3 months vs. 6 months	3 months vs. 12 months	3 months vs. 24 months	12 months vs. 24 months
Central subfield		0.54	**0.044***	0.29	0.89	0.90	0.23	0.39	0.85
Inner superior	**0.0007***	**0.040**	**<0.0001***	**<0.0001***	**<0.0001***	**0.0022***	**0.0061***	**0.0006***	**0.026***
Inner temporal	**<0.0001***	0.60	**<0.0001***	**<0.0001***	**0.0001***	**0.0021***	**0.0077***	**<0.0001***	**0.0007***
Inner inferior	**0.0020***	0.38	**0.022***	**0.0042***	**0.0077***	**0.029***	**0.048***	**0.0073***	**0.0072***
Inner nasal	**0.020***	0.46	0.84	0.44	0.38	0.27	0.23	0.068	0.13
Outer superior	**0.0059†**	0.38	**0.016***	**0.0003***	**<0.0001***	**0.0054***	**0.0009***	**<0.0001***	**0.0038***
Outer temporal	**0.029†**	0.51	0.18	**0.022***	**0.0007***	**0.035***	**0.0002***	**<0.0001***	**0.0048***
Outer inferior	**0.0003†**	0.96	**0.024***	**0.0006***	**0.0007***	**0.0004***	**0.0010***	**<0.0001***	**0.010***
Outer nasal	**0.0004†**	0.46	**0.0023***	**<0.0001***	**<0.0001***	0.16	**0.039***	**0.0052***	**0.0061***

P values are shown. Paired *t*-test was used. Values in bold are significantly different values.
* Significant reduction with time.
† Significant increase with time.

except for the temporal quadrant.[26] As a result, the thicker RNFL covers the ganglion cell layer (GCL) in the outer sectors more than in the inner sectors. In contrast, the GCL is thickest at approximately 1 mm from the foveal center, and gradually becomes thinner as a function of distance from the foveal center in all quadrants.[26] Therefore, thickening of the retina after surgery in the outer sector may be primarily due to the changes in the RNFL thickness, whereas the progressive retinal thinning in the inner sectors may be more attributable to the changes in the inner retinal layers beneath the RNFL, including the GCL.

The changes in the retinal thinning in the inner macular area with increasing postoperative time were different for the four quadrants. The postoperative retinal thinning was most severe in the inner temporal and superior sectors and the least thinning was in the inner nasal sector. The inner temporal sector showed the most progressive retinal thinning, which progressed from 31.6 μm at 1 month to 48.8 μm at 24 months, a change of 17.2 μm. In contrast, the inner nasal sector did not show significant retinal thinning. The regional differences may also be due to the anatomical characteristic of retinal layers in the macula; the RNFL is thinnest in the temporal macula and thickest in the nasal macula, whereas the other retinal layers are almost symmetrical in all quadrants.[26] We suggest that the differences in the RNFL thickness may lead to different responses of the inner macular sectors to the MHS with ILM peeling. The thinner RNFL may be more affected by the MHS with ILM peeling, leading to alterations of the underlying retinal layers. This would cause the most progressive thinning of the temporal macula where the RNFL is thinnest.

The mechanism by which the retina became progressively thinner after successful MHS with ILM peeling remains unclear. It is uncertain whether the ILM peeling is responsible for the progressive changes in retinal thickness, because our study did not include non–ILM-peeled eyes. The ILM is the basement membrane of the Müller cells and is thought to play an important role in the physiology and function of the retina. Damages to the Müller cells have been demonstrated histologically and electroretinographically after ILM peeling.[8–10] Earlier studies showed that 42.6% to 62.2% of the eyes that underwent successful MHS with ILM peeling developed arcuate striae in the extrafoveal retina, which was termed a dissociated optic nerve fiber layer (DONFL) appearance.[11–14] This feature has been attributed to the ILM peeling, because it was found only in the area of the ILM peeling and not found in eyes that had not undergone ILM peeling. It was originally believed that damage of the Müller cells caused the optic nerve fibers to lose their structural support to cause the development of DONFL appearance.[11–14] However, recent studies showed that retinal defects deeper than the RNFL were associated with the arcuate striae in the area where ILM peeling was done.[17,20,21] The inner retinal defects seen on the SD-OCT images have been shown to progress with time.[16,20] Further studies are needed to determine whether these structural changes related to ILM peeling are involved in the progressive retinal thinning after successful MHS.

In our study, the postoperative improvement of visual acuity was good, and none of the eyes had a decrease in the BCVA by more than two lines during the 2-year postoperative follow-up period. It has been established that ILM peeling increases the closure rate of a macular hole, and it does not decrease the visual acuity recovery compared with non-ILM peeling eyes.[3,27–29] The progressive thinning after macular hole closure we observed was limited to the extrafoveal sectors but not found in the central sector (fovea). This may be the reason why visual acuity reduction was not observed during the follow-up in any study eyes. Thus, our findings do not appear to disagree with the consensus that the ILM peeling is a beneficial procedure required for successful MHS.

At the same time, we need to learn whether the progressive retinal thinning causes some adverse effects on the extrafoveal retinal function. Earlier studies reported that there was a decrease of retinal sensitivity associated with the arcuate striae after MHS with ILM peeling by using microperimetry.[30,31] However, other studies did not find any changes in the retinal sensitivities.[13–15] Thus, a reduction of extrafoveal retinal sensitivity after MHS with ILM peeling has not been definitively determined.

A limitation of this study was that we did not determine the retinal sensitivity reduction associated with the progressive retinal thinning. But, the purpose of this study was to determine whether the thinning or thickening of the macula after successful MHS with ILM peeling was transient or progressive. The results provided an answer to this question, but raises the next question on how the progressive retinal thinning in the inner sectors lead to retinal sensitivity changes. We plan to perform a prospective study to answer this question.

Another limitation of this study was the possibility of a mistaken identification of the foveal center, which would lead to inaccurate measurements of the retinal thickness in each of the ETDRS sectors. More specifically, it is uncertain whether the embedded algorithm accurately detects the foveal center in eyes with abnormal foveal shapes before and after the MHS. However, this limitation does not invalidate our finding of a progressive retinal thinning because significant thinning was found in all quadrants except the inner nasal sector.

In conclusion, successful MHS with ILM peeling yielded progressive changes in the retinal thickness in the extrafoveal regions but not in the fovea. The retinal thickening in the outer sectors returned to the preoperative level by 6 to 24 months after surgery, whereas the retina in the inner sectors became progressively thinner for at least 24 months. Further studies are needed to determine whether the progressive retinal thinning causes any adverse effects on extrafoveal retinal function.

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