

Negative correlation between retinal displacement and ganglion cell layer thickness changes in eyes with epiretinal membrane

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Pasquale Loiudice¹ , Marco Pellegrini²,
Andrea Montesel¹ , Marco Nardi¹, Enrico Peiretti³,
Stefano De Cillà⁴, Chiara Posarelli¹, Michele Figus¹ ,
and Giamberto Casini¹

Abstract

Purpose: To examine retinal displacement after vitrectomy with internal limiting membrane peeling for epiretinal membrane treatment, and to determine the correlation between the extent of displacement and the ganglion cell layer thickness changes.

Methods: Thirty-nine consecutive patients were evaluated. Optical coherence tomography was performed preoperatively, and 2 and 6 months postoperatively. The distance between the fovea, the vessel intersection in the superior nasal, superior temporal, inferior nasal, and inferior temporal macular regions, and the optic disk were measured. Ganglion cell layer thickness was recorded.

Results: The distance from the optic disk to the fovea and the superior nasal and inferior nasal vessel intersections significantly reduced at 2 and 6 months. Ganglion cell layer thickness significantly decreased in all the subfields (except nasal) at 6 months. A significant negative correlation was found between the change in the ganglion cell layer thickness and the movement of the fovea toward the optic disk. The ganglion cell layer thickness changes significantly correlated with retinal displacement.

Conclusion: Retinal displacement toward the optic disk was detected after vitrectomy with internal limiting membrane peeling in eyes with epiretinal membrane. Ganglion cell layer thickness significantly reduced in all the subfields (except nasal). The extent of the displacement and the ganglion cell layer thickness changes showed significant negative correlation.

Keywords

Epiretinal membrane, ganglion cell layer, internal limiting membrane peeling, retinal displacement

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Introduction

Idiopathic epiretinal membrane (ERM) is a fibrotic process on the surface of the retina, due to fibrocellular proliferation at the vitreoretinal interface, ranging from a thin translucent layer to a thick opaque membrane.^{1,2} Transdifferentiation of cellular components into myofibroblasts is responsible for the contractile properties of the membrane.^{3,4} As the disease progresses, it causes wrinkling and distortion of the retinal surface and vascular tortuosity. At this stage, ERM is also called macular pucker.

Several authors have described retinal movement due to the contraction of the ERM. Weinberger et al.⁵ used digital

¹Ophthalmology Unit, Department of Surgical, Medical, Molecular Pathology and of Critical Area, University of Pisa, Pisa, Italy

²Ophthalmology Unit, Department of Experimental, Diagnostic and Specialty Medicine, S.Orsola-Malpighi Teaching Hospital, University of Bologna, Bologna, Italy

³Department of Surgical Sciences, Eye Clinic, University of Cagliari, Cagliari, Italy

⁴Department of Health Sciences, Eye Clinic, University of Piemonte Orientale, Novara, Italy

Corresponding author:

Michele Figus, Ophthalmology Unit, Department of Surgical, Medical, Molecular Pathology and of Critical Area, University of Pisa, Via Paradisa 2, 56124 Pisa, Pisa, Italy.
Email: figusmichele@gmail.com

red-free photography to evaluate the displacement of retinal blood vessels during the natural course of ERM formation. Lo et al.⁶ reported foveal dystopia in patients with ERM before surgery and foveal movement toward its expected location postoperatively. Retinal displacement has also been reported after vitrectomy in eyes with macular holes^{7,8} and after retinal detachment surgery.⁹

Patients with ERM are currently treated with pars plana vitrectomy (PPV) and removal of the membrane.¹⁰ Dye-assisted internal limiting membrane (ILM) peeling can reduce the rate of ERM recurrence. ILM peeling ensures complete removal of the fibrocellular membrane and eliminates the scaffold to prevent further proliferation.^{10–12} However, PPV and ILM peeling may influence inner retinal structure, as a reduction in macular ganglion cell-plexiform layer thickness has been reported after vitrectomy for a macular hole, particularly in patients who underwent ILM peeling.¹³

The purpose of this study was to evaluate retinal movements after Brilliant Blue G-assisted (Brilliant Peel[®], Fluoron GmbH, Ulm, Germany) ILM peeling for ERM and to determine whether there was a correlation between the degree of displacement and ganglion cell layer (GCL) thickness changes.

Methods

In this prospective, interventional case series study, we enrolled 39 eyes of 39 consecutive patients diagnosed with ERM and scheduled for surgery. The study received approval from the local Institutional Review Board (Comitato Etico di Area Vasta Nord Ovest, register number: 15255_CASINI), and was conducted in adherence to the tenets of the Declaration of Helsinki. Every patient signed an informed consent form. Eyes with diabetic retinopathy, macular degeneration, myopic chorioretinal atrophy, rhegmatogenous retinal detachment, and any other disease that potentially could interfere with measurements were excluded.

All patients underwent comprehensive ophthalmologic examinations, including measurement of best-corrected visual acuity (BCVA), using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart, intraocular pressure, and slit-lamp biomicroscopy of the anterior and posterior segments. All surgeries were performed by a single surgeon (G.C.) using the Alcon Constellation Ultrahigh-Speed Vitrectomy 25-gauge total pack (Alcon, Fort Worth, TX, United States). A BIOM viewing system (Oculus, Wetzlar, Germany) or a Resight 700 (Carl Zeiss Meditec AG, Jena, Germany) was used for posterior visualization. The surgical treatment included 25-gauge PPV, posterior vitreous detachment, peeling of the ERM, dye-assisted peeling of the ILM using Brilliant Blue G, and air–fluid exchange. The stained ILM was peeled to the edge of the vascular arcade using an end-gripping forceps

(Grieshaber Asymmetrical Forceps, DSP, Alcon, Fort Worth, TX, United States). All patients remained in prone position for 48 h after surgery. Phakic patients underwent cataract surgery at the same time as the vitrectomy.

Spectral-domain optical coherence tomography (SD-OCT, Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany) was performed preoperatively, and 2 and 6 months after surgery. Infrared images were used to calculate the relative positions of optic disk, fovea, and retinal vessels. Using the caliper function, we measured the distance between the point at which the central retinal vein emerges from the optic disk and the center of the fovea, and the distance between the optic disk and vessel intersection in the superior nasal, superior temporal, inferior nasal, and inferior temporal macular regions (Figure 1).

The GCL thickness was calculated using the segmentation tool of the instrument. All the segmentations were carefully checked and manually adjusted when needed. Unreliable images were excluded from the analysis. The macular area was divided in nine subfields according to the ETDRS grid: foveal, inner superior, inner inferior, inner temporal, inner nasal, outer superior, outer inferior, outer temporal, and outer nasal (Figure 2).

Statistical analysis was performed using IBM SPSS software (IBM, NY, United States). The distribution of data was assessed using Kolmogorov–Smirnov test and Shapiro–Wilk test. The Wilcoxon test was used to determine whether differences over time were significant. The correlations between the degree of displacement and GCL thickness changes were evaluated using Spearman rank correlations. Differences were considered significant when $P < 0.05$.

Results

In this prospective observational study, 39 eyes of 39 patients (21 male and 18 female) were consecutively enrolled. Mean age was 69.35 ± 0.7 years. Of the 39 patients, 15 (38.46%) were phakic and underwent combined phacovitrectomy.

Table 1 shows the median of the distances from the optic disk to the fovea, and to the superior nasal, superior temporal, inferior nasal, and inferior temporal vessel intersections before surgery, and 2 and 6 months after surgery. Two months after surgery, the median of the distance from the optic disk to the fovea was reduced by $100 \mu\text{m}$ (–3%) compared with preoperative values, and the median of the distances between the fovea and the superior nasal, inferior nasal, superior temporal, and inferior temporal vessel intersections were increased by $94 \mu\text{m}$ (4%), $117 \mu\text{m}$ (7%), and $193 \mu\text{m}$ (9%), compared with preoperative values. The reduction in distance between the optic disk and the fovea and between the optic disk and the superior nasal and inferior nasal vessel intersections were statistically significant ($P = 0.008$, $P = 0.037$, and $P = 0.005$, respectively, Wilcoxon

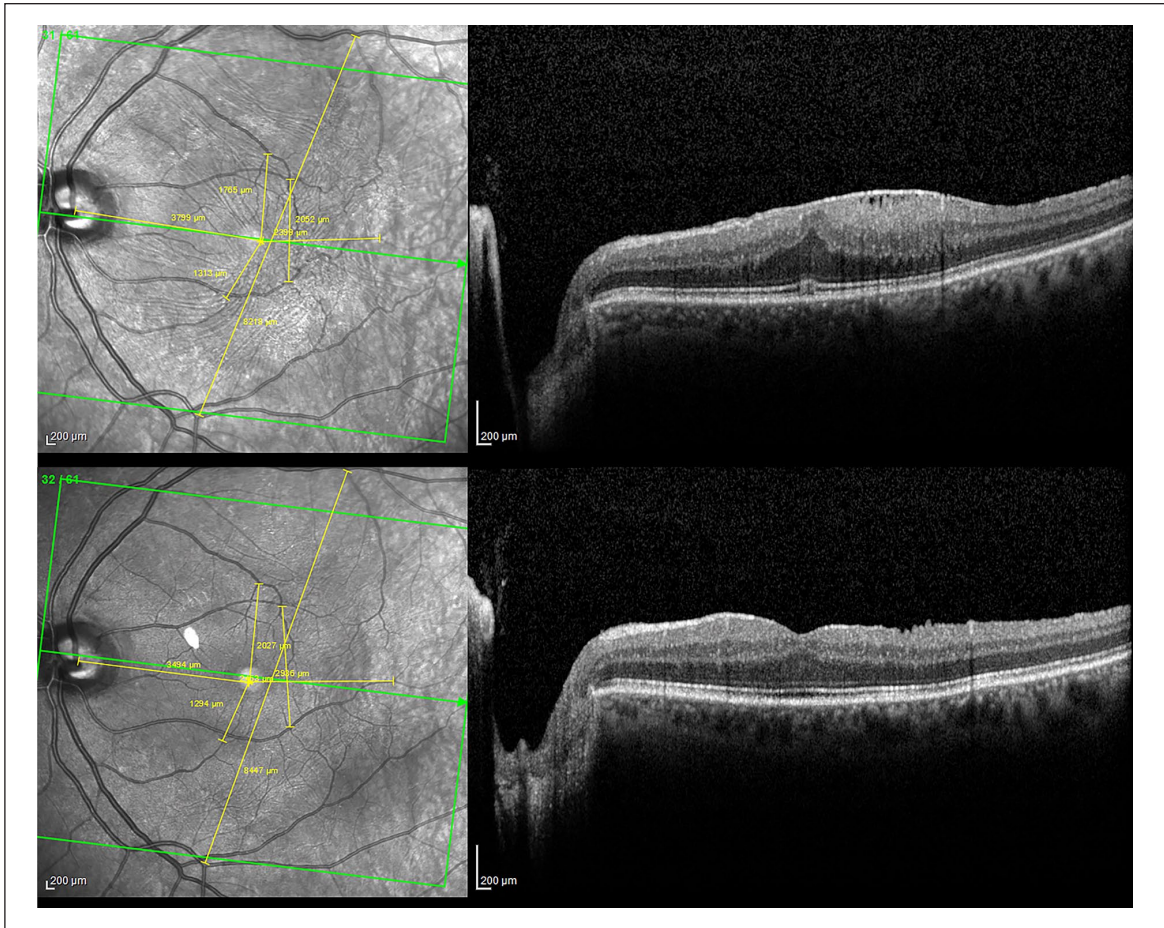


Figure 1. Fundus infrared images and spectral-domain optical coherence tomographic images in a patient with idiopathic epiretinal membrane. The distance from the optic disk to the fovea and from the optic disk to the vessel intersection in the superior nasal, inferior nasal, superior temporal, and inferior temporal macular regions were manually measured, preoperatively (upper left) and 6 months after surgery (lower left).

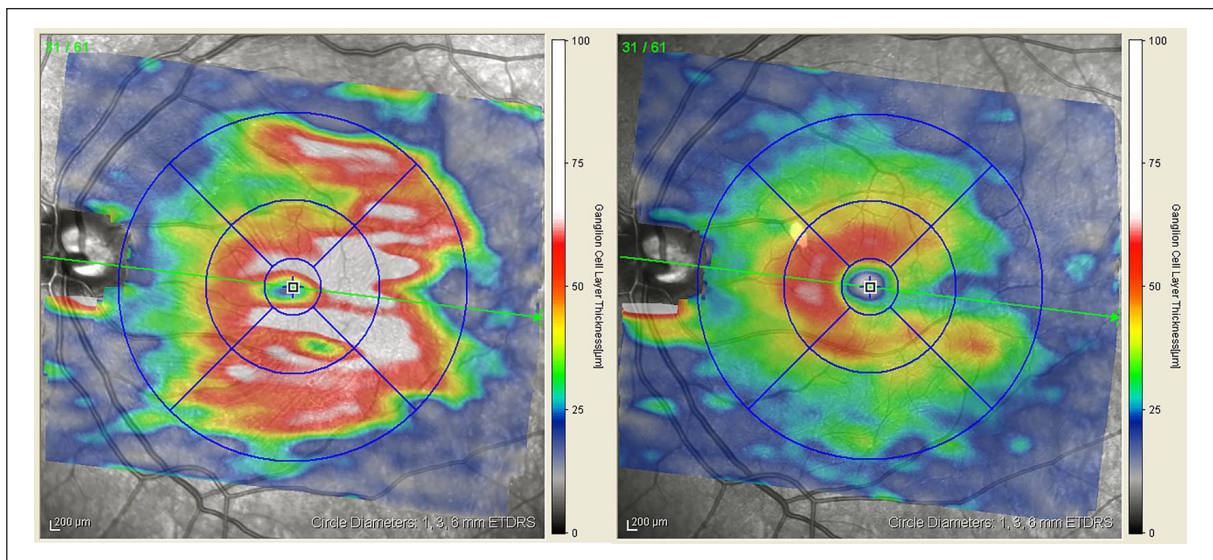


Figure 2. Ganglion cell layer thickness preoperatively (left) and 6 months (right) after vitrectomy with inner limiting membrane peeling for epiretinal membrane. The macular region was divided in nine subfields according to Early Treatment Diabetic Retinopathy Study grid.

Table 1. Retinal measurements.

Distance	T0	T1	<i>P</i> ^a	T2	<i>P</i> ^b
F-OD	3485 (2989–4342)	3384 (2932–3970)	0.002	3257 (2895–3946)	0.001
F-SUP	2156 (1442–2850)	2250 (1499–3470)	0.049	2375 (1462–3824)	0.035
F-INF	1648 (836–2777)	1765 (1019–2829)	0.046	1879 (1017–2929)	0.025
F-TEMP	3084 (1941–3668)	3277 (1972–3931)	0.018	3419 (1891–4167)	0.003
MIN	3117 (1883–4440)	3189 (2234–5217)	0.003	3206 (2342–5339)	0.004
MAJ	7595 (5153–8615)	7778 (5292–8581)	0.026	7899 (5394–8573)	0.016

Distances (μm) from the fovea (F) to the optic disk (OD) and from the F to the vessel intersection in the superior (SUP), inferior (INF), temporal (TEMP) macular region, distance between minor vessel branches (MIN) and major vessel branches (MAJ) at baseline (T0), 2 months (T1) and 6 months (T2) after surgery. Values are median (minimum–maximum).

^a2 months after surgery compared to baseline with Wilcoxon test.

^b6 months after surgery compared to baseline with Wilcoxon test.

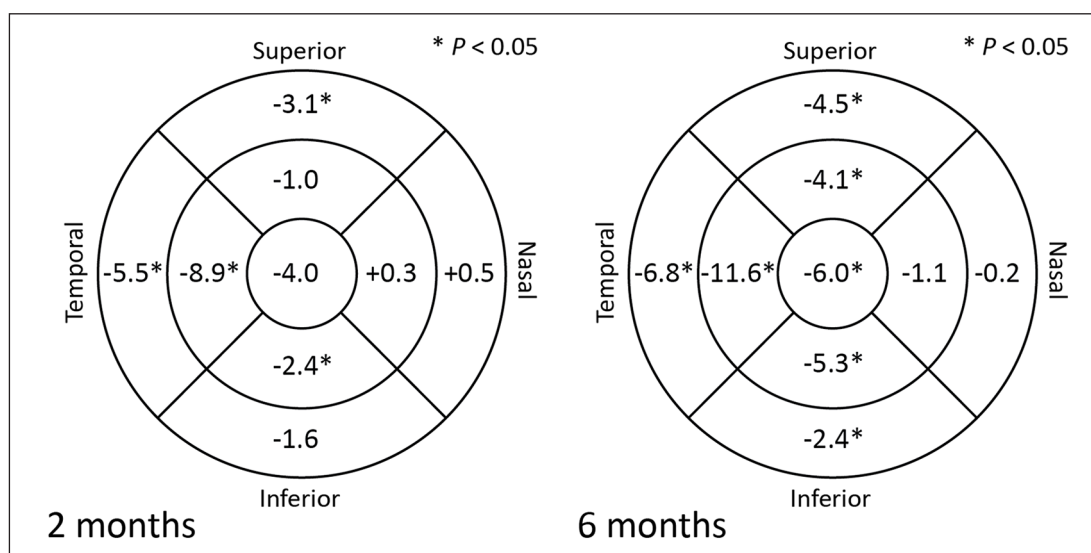


Figure 3. Mean changes in the ganglion cell layer thickness at 2 and 6 months after epiretinal membrane surgery compared with preoperative values. Asterisks indicate $P < 0.05$ (Wilcoxon tests).

T0=baseline; T1=2 months postoperatively; T2=6 months postoperatively.

test). Six months after surgery, the mean distance between the optic disk and the fovea was reduced by $166 \mu\text{m}$ (4.8%) compared with preoperative values, and the distance from the optic disk to the superior nasal, inferior nasal, superior temporal, and inferior temporal vessel intersections was reduced by $62 \mu\text{m}$ (2.2%), $75 \mu\text{m}$ (2.8%), $35 \mu\text{m}$ (1.5%), and $18 \mu\text{m}$ (0.3%), respectively, compared with preoperative values. The reduction in distance from the optic disk to the fovea and from the optic disk to the superior nasal and inferior nasal vessel intersections were statistically significant ($P=0.006$, $P=0.043$, and $P=0.039$, respectively, Wilcoxon test).

Table 2 shows the mean GCL thickness in nine macular subfields before surgery, and 2 and 6 months after surgery. The mean changes in the GCL thickness 2 and 6 months after surgery compared with preoperative values are shown in Figure 3. Two months after surgery, the GCL thickness significantly decreased in the outer temporal,

inner temporal, outer superior, and inner inferior macular subfields compared with preoperative values ($P < 0.001$, $P < 0.001$, $P=0.043$, and $P=0.039$, respectively, Wilcoxon test). Six months after surgery, the GCL thickness significantly decreased in the fovea and in the outer temporal, inner temporal, outer superior, inner superior, outer inferior, and inner inferior macular subfields compared with preoperative values ($P=0.004$, $P < 0.001$, $P < 0.001$, $P=0.001$, $P=0.024$, $P=0.039$, and $P=0.004$, respectively, Wilcoxon test).

Postoperative GCL thinning was notably higher in the temporal section. Before surgery, the mean nasal GCL thickness was $40.9 \pm 6.8 \mu\text{m}$ and the mean temporal GCL thickness was $41.3 \pm 8.1 \mu\text{m}$, which was not a statistically significant difference ($P=0.797$, Wilcoxon test). However, 2 months after surgery, a statistically significant difference of $6.7 \pm 8.4 \mu\text{m}$ was found between the mean nasal and the mean temporal GCL thickness ($P < 0.001$, Wilcoxon test).

Table 2. Ganglion cell layer measurements.

	T0	T1	<i>P</i> ^a	T2	<i>P</i> ^b
Central	32 (9–65)	30 (13–60)	0.091	28.5 (13–59)	0.004
Outer nasal	32.5 (20–40)	32 (24–41)	0.507	32 (22–46)	0.686
Inner nasal	47.5 (26–68)	49 (27–67)	0.957	48 (25–73)	0.808
Outer temporal	30 (18–62)	28 (17–54)	<0.001	27 (17–47)	<0.001
Inner temporal	44.5 (27–67)	36.5 (16–57)	<0.001	35.5 (16–58)	<0.001
Outer superior	30 (24–54)	28.5 (20–44)	0.043	28 (20–37)	0.001
Inner superior	49.5 (23–67)	45.5 (23–66)	0.588	43 (23–66)	0.024
Outer inferior	28.5 (21–48)	27 (21–32)	0.560	26.5 (11–34)	0.039
Inner inferior	48 (10–65)	46 (27–62)	0.039	42 (25–60)	0.004

Ganglion cell layer thickness (μm) in the foveal, outer nasal, inner nasal, outer temporal, inner temporal, outer superior, inner superior, outer inferior, and inner inferior macular area before surgery (T0), 2 months (T1), and 6 months (T2) postoperatively. Values are median (minimum–maximum).

^a2 months after surgery compared to baseline with Wilcoxon test.

^b6 months after surgery compared to baseline with Wilcoxon test.

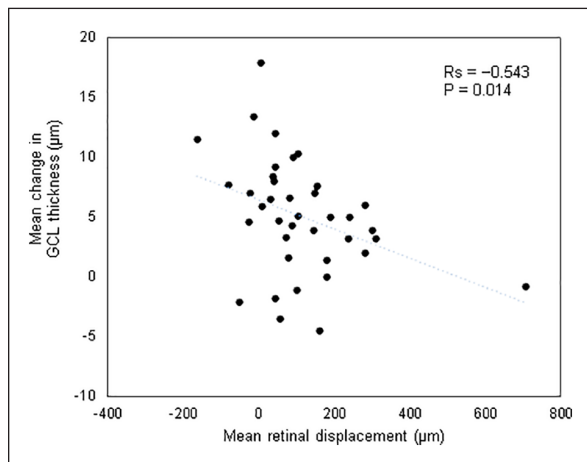


Figure 4. Scatter plot graph showing negative correlation between mean change in ganglion cell layer thickness and mean retinal displacement.

This difference increased to $7.7 \pm 8.2 \mu\text{m}$ at 6 months after surgery ($P=0.001$, Wilcoxon test).

In the postoperative period, we observed two cases of macular edema. Central macular thickness was 280 and 341 μm , respectively. The patients were treated with intravitreal injection of triamcinolone acetonide (Taoifal®, SOOFT S.p.A., Italy). The edema was completely resolved at the last follow-up. No other complications occurred.

A Spearman correlation was performed to determine the relationship between the movement of the retina toward the optic disk and the change in the GCL thickness. A significant negative correlation was found between the change in the GCL thickness in the inner temporal area and the movement of the fovea toward the optic disk ($P=0.024$; $R=-0.379$). Moreover, the mean of the GCL thickness changes in all the subfields was significantly correlated with the mean of the retinal displacement in all the measured areas ($P=0.014$; $R=-0.543$) (Figure 4).

Discussion

Patients with ERM experience progressive worsening of visual function due to the thickening and contraction of the membrane and the distortion of the underlying retina. These modifications may result in metamorphopsia and loss of central vision. Arimura et al.¹⁴ found a correlation between the severity of metamorphopsia and retinal contraction in eyes with ERM. In cases of ERM, the contraction of the membrane dislocates the photoreceptors and the outer retinal layer, with consequent metamorphopsia that can still be present even after surgically successful ERM peeling and visual acuity improvement.¹⁵

Topographic modifications of retinal vessels have previously been observed in eyes with ERM.^{5,16,17} In our study, we observed that the retina in the macular area moved toward the optic disk after PPV and ILM peeling. We found a significant reduction in distance between the optic disk and the fovea, and between the optic disk and the superior nasal and inferior nasal vessels. No significant change was observed in the temporal area.

This is not completely in accordance with previous studies. Retinal displacement toward the optic disk was previously reported after PPV with ILM peeling for macular hole⁷; however, Ishida et al.⁸ reported that the temporal vessels moved more than the nasal ones. In a comparative study of retinal displacement after surgery for macular hole and ERM, Rodrigues et al.¹⁸ found relative retinal expansion after ERM removal and contraction after macular hole closure, due to, respectively, centrifugal and centripetal forces acting on the retina after surgery. Using red-free digital photography, Weinberger et al.⁵ studied the displacement of retinal blood vessels during the natural course of ERM formation. They found that the distances between vascular arcades may either increase or decrease or show a mixed pattern. To avoid this possible bias, in our study, we use the fovea as a landmark, and we measured the relative distance between the fovea and the optic disk and the

vascular arcade. In this way, we were able to independently measure the re-arrangement forces according with the direction in which they were acting. Centrifugal movements have been observed in eyes with ERM due to multiple foci of retinal traction.¹⁷

A possible explanation for similar behavior may be found if we consider the optic disk as a fulcrum or an anchor point for the retina. Under the action of the ERM, the retinal surface contracts and distorts. The removal of the ERM modifies the tangential stress forces, so the retina may relax and recover to its original arrangement.¹⁹ Since the optic disk is a fixed point, the retina behaves like a spring and displacement movements are more evident in foveal and nasal regions. This also explains why retinal dislocation was not significant in the temporal area. Kawano et al.⁷ hypothesized that, in cases of macular hole, ILM peeling was likely to cause retinal movement. They suggested that the ILM peeling may alter the forces acting on the retina, and since there is no ILM on the optic disk, the fovea was displaced nasally.

Progress in SD-OCT technology has made it possible to obtain high-resolution retinal images; furthermore, the development of a segmentation tool in the software enables a layer-by-layer analysis.^{20,21} A high reproducibility of the measurements of the retinal ganglion cell-inner plexiform layer using SD-OCT in both normal and glaucomatous eyes has been previously reported.²²⁻²⁴ Auto-segmentation has also shown high repeatability in eyes with ERM and central macular thickness less than 450 μm .²⁵

Examination of each retinal layer has increasingly gained interest since a correlation between inner retinal layer and retinal sensibility was reported.²⁶ Postoperative visual acuity has been reported to be related to the thickness of the inner retinal layer and changes in the GCL.^{27,28} Baba et al.²⁶ observed a reduction in the thickness of the ganglion cell complex after vitrectomy with ILM peeling in eyes with idiopathic macular hole (IMH).

Peeling the ILM is an effective and widely performed procedure that offers numerous advantages. It ensures complete removal of the ERM and is associated with an increase in closure rate in macular hole surgery, by removing a potential scaffold for cell migration.²⁹ However, several authors have reported that the retina may be affected by ILM peeling. ILM peeling has been reported to result in defects of the inner retina, as evidenced by an increase in the dissociated optic nerve fiber layer appearance.³⁰⁻³² Decreased retinal sensitivity,³³ microscotomas,³³ swelling of the arcuate retinal nerve fiber layer,³⁴ and reduction of the thickness of the ganglion cell complex²⁶ have also been associated with ILM peeling.

In our study, the GCL thickness significantly reduced in the outer temporal, inner temporal, outer superior, and inner inferior subfields at 2 months postoperatively and in all sectors except the nasal ones at the last follow-up. This indicates that retinal modifications continued up to 6 months after surgery.

Postoperative GCL thinning was notably higher in the temporal section and the difference in thickness between the mean temporal and the nasal GCL increased at 2 months and further decreased at 6 months postoperatively, despite no statistically significant difference at baseline. Sevim and Sanisoglu³⁵ reported no differences in the thickness of the GCL in eyes with IMH after Brilliant Blue G-assisted ILM peeling. In contrast, Baba et al.²⁶ reported a reduction in thickness of the ganglion cell complex after vitrectomy and ILM peeling in patients with IMH.

In their retrospective study, Won et al.³⁶ reported a reduction in GCL thickness in the foveal, inner superior, inner temporal, and outer nasal subfields after vitrectomy and ILM peeling for ERM. Lim et al.³⁷ studied the effect of vitrectomy in eyes without vitreoretinal disease and found that the thickness of the macula and ganglion cell-inner plexiform layer increased at 1 month postoperatively, after which it returned to preoperative values. These findings are thought to be due to vitreoretinal inflammation caused by the surgery.

The pathogenesis of the GCL modifications has not been fully explained and is currently debated. Mechanical damage induced by forceps during ILM peeling, inflammatory distress, and trophic action carried out by ILM toward the ganglion cells have been hypothesized to have a role in GCL modifications after surgery.^{36,37} Another explanation would be a loss of traumatized Müller cells contained in the GCL, as the endfeet of Müller cells are removed with the ILM peeling.^{38,39}

However, GCL changes could be affected by retinal movements that occur after surgery. In our study, we found a significant correlation between retinal displacement and GCL thickness. In other words, the correlation between the mean retinal displacement and the mean GCL thickness change was significant and negative, which indicates that the greater the displacement, the less the GCL thickness decrease. A significant negative correlation was also found between the GCL thickness change in the inner temporal area (the area in which the greatest reduction occurred) and foveal displacement, which was the greater displacement. To the best of our knowledge, no previous studies have analyzed a similar correlation. A possible explanation for this behavior was discussed as follows. It is believed that retinal movements occur at the interface between the retinal pigment epithelium (RPE) and retina, as demonstrated by hyperautofluorescent lines running parallel to major blood vessels, visible on fundus autofluorescence imaging. We observed that in some patients, the retina became less mobile, probably due to a greater adhesion to the RPE. In these cases, the tension forces that drive retinal arrangement after surgery resulted in stretching of the inner retina with resulting decrease in GCL thickness. In eyes with a more mobile retina and a greater displacement after ILM peeling, the stress forces were lower, with consequent lower impact on the GCL.

In conclusion, we found retinal displacement toward the optic disk after vitrectomy with Brilliant Blue G-assisted ILM peeling in eyes with ERM. The GCL thickness significantly reduced in all the ETDRS subfields except the nasal ones, with the greatest reduction in the temporal area. There was a significant negative correlation between the extent of the displacement and the GCL thickness changes.

Declaration of conflicting interests

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ORCID iDs

Pasquale Loiudice  <https://orcid.org/0000-0001-8529-9897>

Andrea Montesel  <https://orcid.org/0000-0002-1910-9976>

Michele Figus  <https://orcid.org/0000-0003-2243-9033>

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