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Evaluation of Macular Function Using Microperimetry and Multifocal Electroretinograms in Macular Hole Surgery

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ABSTRACT
Objective: To investigate the outcomes of internal limiting membrane (ILM) peeling using microperimetry (MP) and multifocal electroretinogram (mfERG) instruments. **Material and Methods:** Forty-two eyes of 42 patients with ILM peeling were evaluated. Unity of outer stratums was assessed using spectral-domain optic coherence tomography. MfERG parameters (N1 and P1 amplitude, implicit time) and MP parameters were also measured both at baseline and month-12. **Results:** The mean P1 amplitude in ring 1 increased according to the baseline value (p=0.002). However, the mean P1 amplitudes were lower compared with baseline values in mfERG in rings 2, 3, 4, and 5 (p = 0.016 for ring 2 and p < 0.001 for other rings). According to the preoperative retinal sensitivity of each of 37-point in MP, there was a reduction of 22.1% at month-12 in the ILM peeling area, and absolute microscotomas were detected in two points of two eyes at month-12. Metamorphopsia was associated with disrupted ellipsoid zone at month-12 (OR=6.75, p=0.008). **Conclusion:** The potential risk of a decrease in postoperative macular sensitivity should be taken into consideration if ILM peeling is planned in macular hole surgery.
Keywords: Internal Limiting Membrane Peeling, Macular Hole Surgery, Microperimetry, Multifocal Electroretinogram, Metamorphopsia, Spectral-Domain Optic Coherence Tomography.

Makula Deliği Cerrahisinde Makula Fonksiyonunun Mikroperimetri ve Multifokal Elektroretinogram ile Değerlendirilmesi

ÖZ
Amaç: Çalışmanın amacı, mikroperimetri (MP) ve multifokal elektroretinogram (mfERG) cihazları ile iç limitan membran (İLM) soyulmasının etkilerini araştırmaktır. **Gereç ve Yöntem:** İç limitan membranı soyulan 42 hastanın 42 gözü değerlendirildi. Spektral alan optik koherens tomografi kullanılarak dış katmanların bütünlüğü ölçüldü. MfERG parametreleri (N1 ve P1 genliği, implisit zamanı) ve MP parametreleri de hem başlangıç hem de 12. ayda ölçüldü. **Bulgular:** Halka 1'deki P1 genliklerinin ortalaması ameliyat öncesi değere göre arttı (p=0.002). Ancak, ameliyat sonrası ortalama P1 genlikleri halka 2, 3, 4 ve 5'te mfERG'deki başlangıç değerlerine göre azaldığı tespit edildi (halka 2 için p=0.016 ve diğer halkalar için p < 0.001). MP'de 37 noktanın başlangıç retina duyarlılığına göre, 12. ayda İLM soyma bölgesinde %22.1 azalma ve 12. ayda iki gözde iki noktada mutlak mikroskotom tespit edildi. Metamorfopsi şikayeti 12. ayda ellipsoid zonun bozulması ile ilişkiliydi (OR=6.75, p=0.008). **Sonuç:** Makula deliği cerrahisinde İLM soyulması planlanıyorsa, postoperatif makula duyarlılığında olası azalma riski göz önünde bulundurulmalıdır.
Anahtar Kelimeler: İç Limitan Membran Soyulması, Makula Deliği Cerrahisi, Mikroperimetri, Multifokal Elektroretinogram, Metamorfopsi, Spektral Alan Optik Koherens Tomografi.

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INTRODUCTION

Internal limiting membrane (ILM) peeling was first introduced to improve anatomic outcomes in idiopathic full-thickness macular hole (FTMH) surgery (Eckardt C et al., 1997). Since then, ILM peeling has become the gold standard procedure with over a 90% anatomic success rate (Yao Y et al., 2019). Despite the high anatomic success rates, functional outcomes remain unsatisfactory in some cases. Functional outcomes after FTMH surgery are generally evaluated using visual acuity, which hinges upon the susceptibility of the fovea. However, this symbolizes just a component of visual function, which includes metamorphopsia, sensitivity, and scotoma.

ILM peeling was reported to have a negative effect on the optic nerve fiber sheet of the retina. This effect was first termed as "dissociated optic nerve fiber layer (DONFL)" by Tadayoni (Tadayoni R et al., 2001). In addition, shrinkage and displacement of the ganglion cell axons and neural layer may cause alterations in the anatomy of outer retinal stratums (Faria MY et al., 2018). Reduced macular electrical potential or sensitivity may result in reduced visual function despite achieving anatomic success after FTMH surgery.

Sutter and Tran introduced multifocal electroretinogram (mfERG) to supply a topographic scheme of macular electrophysiologic function (Sutter EE & Tran D, 1992). Microperimetry (MP) is an objective analysis method that can be used to evaluate the susceptibility of the macula at specific points. It reveals relative and absolute microscotomas.

The aim of this retrospective research was to define macular function using MP and mfERG, before and after ILM peeling.

MATERIALS AND METHODS

Study type

Forty-two eyes of 42 patients who underwent ILM peeling from July 2014 to June 2019 were evaluated. All patients underwent a detailed ophthalmic evaluation including best corrected visual acuity (BCVA), spectral-domain optical coherence tomography (SD-OCT) imaging using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), MP (MAIA, Centervue SpA, Padova, Italy), and mfERG (RetiSCAN system, Roland Consult, Wiesbaden, Germany) at baseline and month-12. Self-reported presence of metamorphopsia at month-12 was recorded for all patients. If the patient reported distortions in the size and shape of objects, subjective perception of metamorphopsia was determined as positive. The minimum follow-up was 12 months.

Exclusion Criteria

Eyes with unsuccessful hole closure, high myopia (an axial length > 26.5 mm), history of trauma, and any retinal vascular pathologies (diabetic retinopathy, retinal vein occlusion, vasculitis) were excluded.

Measurement of SD-OCT, MP, and mfERG

The minimum hole diameter was evaluated using a manual caliper on the horizontal B-scans of the SD-OCT. The anatomy of the ellipsoid zone (EZ) and the external limiting membrane (ELM) were classified as disrupted depending on whether the layers appeared blurred or interrupted on at least one B-scan SD-OCT image at month-12. The disruption diameters of EZ and ELM were evaluated using a manual caliper, and the largest measurements were included. Based on the MP findings, we evaluated the average threshold (AT), macular integrity index (MI), fixation stability P1 and P2, and changes of retinal sensitivity of 37 points in eyes that underwent ILM peeling. The mfERG evaluation was made in accordance with the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV). The amplitude and implicit time of N1 and P1 in the foveal, parafoveal, and perifoveal rings were recorded.

Surgical technique

All patients underwent surgery by the same surgeon (S.Y.) using a 23 G PPV system (DORC) (Dutch Ophthalmic Research Center, Zuidland, The Netherlands). Small-incision phacoemulsification (Alcon Infiniti Vision System with Ozil IP) and lens implantation were performed on 23 patients at the same time. The ILM was totally removed in a circular fashion at least a 1.5-disc radius from the hole.

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normality of the distribution of the variables. Parametric tests were used to compare the parameters at baseline and month-12. Pearson or Spearman rank correlation tests were used to reveal the strength and direction of association between two parameters. The analysis of categorical data in cross-tables was performed using the Chi-square test or Fisher's exact test. Linear regression was performed using the forward method to predict the BCVA at month-12 from the baseline BCVA, SD-OCT, mfERG, and MP parameters. Also, for associations between postoperative metamorphopsia symptoms and SD-OCT, MP, and mfERG parameters, the Spearman rank correlation test and binary logistic regression were used. A p-value of < 0.05 was evaluated as significant. All analyses were performed using the IBM SPSS Statistics for Windows package, version 21.0 (IBM Corp, Armonk, NY).

Ethic approval

This was a retrospective, observational, single-center study. The plan and management of the research complied with the common basis outlined in the Declaration of Helsinki and adhered to the basis of Good Clinical Practice. The research was affirmed by the Ethics Committee of Uludağ University Faculty of Medicine, Bursa, Turkey (2021-10/38) before the study period.

RESULTS

The mean age of the patients was 67.40 ± 5.96 (range, 52-83) years and the mean minimum hole diameter was 498.17 ± 204.54 (range, 161-917) µm. The mean baseline BCVA improved from 1.05 ± 0.47 (range, 1.8-0.3) logMAR to 0.31 ± 0.26 (range, 1.0-0) logMAR at month

12 (p < 0.001). Baseline and postoperative month-12 MP and mfERG data are shown in Table 1. The mean follow-up was 29.36 ± 14.35 (range, 12-60) months. None of the patients require a second surgery during the follow-up.

Table 1. Microperimetry and mfERG data baseline and month-12.

	Baseline (n = 42) mean ± SD	**Month-12 (n = 42) mean ± SD**	**p**
Microperimetry			
MI (%)	92.93±14.25	79.75±19.87	**< 0.001***
AT (dB)	20.86±5.45	24.65±3.61	**< 0.001***
Fix. Sta. P1 (%)	57.83±34.19	78.48±29.72	**0.003***
Fix. Sta. P2 (%)	81.29±25.61	91.14±20.28	0.05*
MfERG Ring 1			
N1 amp. (nV/deg^2)	33.81±22.51	38.89±9.51	0.202*
N1 imp. time (ms)	28.14±3.06	28.88±1.58	0.126*
P1 amp. (nV/deg^2)	57.56±14.15	72.73±28.73	**0.002***
P1 imp. time (ms)	51.12±4.97	49.65±0.80	0.079*
MfERG Ring 2			
N1 amp. (nV/deg^2)	15.24±3.08	15.13±4.57	0.912*
N1 imp. time (ms)	27.21±1.51	26.95±1.04	0.349*
P1 amp. (nV/deg^2)	45.97±15.76	39.94±8.78	**0.016***
P1 imp. time (ms)	45.57±1.75	47.10±1.38	**< 0.001***
MfERG Ring 3			
N1 amp. (nV/deg^2)	8.53±1.88	10.01±3.57	0.626*
N1 imp. time (ms)	24.55±1.24	26.15±1.85	**< 0.001***
P1 amp. (nV/deg^2)	30.70±6.59	23.20±5.44	**< 0.001***
P1 imp. time (ms)	43.43±1.59	45.35±1.52	**< 0.001***
MfERG Ring 4			
N1 amp. (nV/deg^2)	6.11±1.32	5.46±2.55	0.108*
N1 imp. time (ms)	26.06±0.92	26.94±2.40	**0.046***
P1 amp. (nV/deg^2)	18.95±3.27	13.98±3.01	**< 0.001***
P1 imp. time (ms)	44.88±1.96	45.65±1.16	**0.024***
MfERG Ring 5			
N1 amp. (nV/deg^2)	5.02±1.66	4.94±1.23	0.826*
N1 imp. time (ms)	27.03±1.46	27.75±1.58	**0.049***
P1 amp. (nV/deg^2)	14.13±2.59	11.80±2.07	**< 0.001***
P1 imp. time (ms)	45.65±1.60	48.10±1.87	**< 0.001***

SD=Standard deviation, **MI**= % macular integrity (0 - 40: Normal, 40 - 60: Suspect, 60 - 100: Abnormal), **AT**=Average threshold (36 - 25: Normal, 25 - 23: Suspect, 23 - 0: Abnormal), **dB**=Decibel, *Fix. Sta.* **P1**=% within 2 degree fixation (> 2/3: Stable, 1/3 - 2/3: Relative unstable, < 1/3: Unstable), **Fix. Sta. P2**=% within 4-degree fixation (> 2/3: Stable, 1/3 - 2/3: Relative unstable, < 1/3: Unstable), **MfERG**=Multifocal electroretinogram, **N1**=The first negative peak, **Amp**=Amplitude, **nV/deg^2**= Nanovoltage/area degree^2, *Imp. time,* Latency, **ms**=Milliseconds, **P1**=The first positive peak.
*Paired t test.

SD-OCT, MP, and mfERG outcomes

SD-OCT. The mean disruption lengths of EZ (16 eyes) and ELM (12 eyes) at month 12 were 261.94±226.60 (range, 35-915) µm and 280.50±212.21 (range, 69-743) µm respectively. Also, there was a significant correlation between the disrupted EZ band and BCVA at month 12 (rs =-0.356 and p=0.021).

MP. There was a significant correlation between the minimum hole diameter and baseline (rp=-0.629 and p<0.001) and month 12 AT (rp=-0.400 and p = 0.009). Furthermore, there was a significant correlation between baseline AT and both baseline (rp=0.551 and p < 0.001) and month-12 BCVA (rp = 0.495 and p = 0.001). Retinal susceptibility in the ILM peeling area increased in 52.6% of patients, unchanged in 25.3%, and reduced in 22.1% of patients at month 12 (Figure 1). In addition, absolute micro scotomas were detected in two points of two eyes at month 12 (Figure 2).

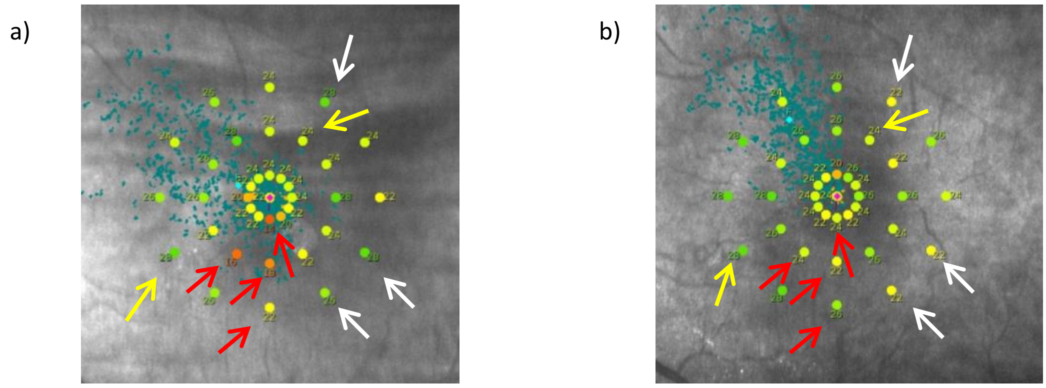

Figure 1. The baseline (a) and month 12 (b) MP images of the same patient. Increased (red arrow), unchanged (yellow arrow), and reduced (white arrow) retinal sensitivity was detected.

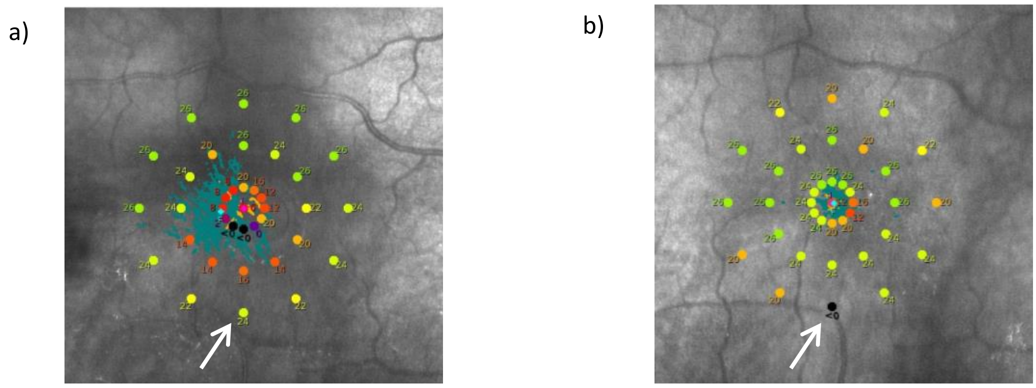

Figure 2. The baseline (a) and month 12 (b) MP images of the same patient. Despite the baseline value of the marked point (white arrow) was 24 dB, an absolute microscotoma was detected at the same point 12 months after the ILM peeling.

MfERG. A significant correlation was detected between the minimum hole diameter and both N1 implicit time of ring 1 (rp=0.355 and p=0.021) and P1 amplitude of ring 1 at month 12 (rp=-0.424 and p=0.005) Moreover, a significant correlation was detected between the month-12 BCVA and baseline N1 amplitude of ring 1 (rp=-0.358 and p=0.020), N1 amplitude of ring 1 at month 12 (rp=-0.364 and p=0.018), N1 implicit time of ring 1 at month 12 (rp=0.647 and p<0.001), P1 amplitude of ring 1 at month 12 (rp=-0.815 and p<0.017), and P1 implicit time of ring 1 at month 12 (rp=0.372 and p=0.015).

BCVA. Using the minimum hole diameter, baseline AT, and mfERG ring 1 P1 and N1 amplitudes, the linear regression model with the forward method for BCVA at month 12 prediction was as follows: BCVA at month 12 (in logMAR)=-0.70 + 0.001 * minimum hole diameter. The R-values and the standard error of the estimate were respectively 0.594 and 0.22.

Metamorphopsia. Twelve of the 16 patients with a disrupted EZ band and eight of the 26 patients with an intact EZ band had symptoms of metamorphopsia (p = 0.005). Binary logistic regression analysis indicated that metamorphopsia was associated with disruption of the EZ band (OR=6.75, p=0.008) (Table 2).

Table 2. Comparisons of the microperimetry, mfERG, minimum hole diameter, and best corrected visual acuity with regard to the ellipsoid zone integrity and metamorphopsia.

	Ellipsoid Zone			Metamorphopsia		
	Intact (mean±SD) (n=26)	**Disrupted (mean±SD) (n=16)**	**p**	**Absent (mean±SD) (n=22)**	**Present (mean±SD) (n=20)**	**p**
MHD	415±172.13	633.31±183.04	**< 0.001***	486.73±205.23	510.75±208.35	0.709*
Baseline BCVA (logMAR)	0.9 ±0.41	1.26±0.51	**0.022***	0.97±0.48	1.15±0.47	0.232*
BCVA at month-12 (logMAR)	0.23±0.19	0.44±0.33	**0.014***	0.25±0.23	0.38±0.29	0.112*
Microperimetry (Baseline)						
MI (%)	90.83±14.98	96.35±12.68	0.227*	90.86±15.44	95.21±12.81	0.330*
AT (dB)	22.64±3.74	17.98±5.60	**0.006***	21.09±5.69	20.62±5.31	0.786*
Fix. Sta. P1 (%)	64.58±34.63	46.88±31.45	0.104*	58.23±36.86	57.40±31.95	0.939*
Fix. Sta. P2 (%)	83.31±26.96	78.00±23.72	0.521*	79.55±26.80	83.20±24.78	0.650*
Microperimetry (At month-12)						
MI (%)	75.17±20.36	87.19±17.10	**0.047***	71.94±19.52	88.34±16.80	**0.006***
AT (dB)	25.12±4.16	23.87±2.39	0.282*	25.22±4.45	24.02±2.35	0.284*
Fix. Sta. P1 (%)	79.15±31.62	77.38±27.32	0.853*	74.95±33.17	82.35±25.70	0.427*
Fix. Sta. P2 (%)	90.69±20.74	91.88±20.17	0.857*	88.82±22.12	93.70±18.27	0.443*
MfERG Ring 1 (Baseline)						
N1 amp. (nV/deg^2)	40.00±20.88	23.75±22.00	**0.021***	38.26±23.15	28.92±21.29	0.183*
N1 imp. time (ms)	28.65±3.03	27.31±3.03	0.170*	28.18±2.94	28.10±3.28	0.932*
P1 amp. (nV/deg^2)	59.32±13.33	54.71±15.67	0.312*	57.86±13.75	57.23±14.92	0.887*
P1 imp. time (ms)	51.49±3.52	50.53±6.83	0.550*	51.15±3.73	51.10±6.19	0.974*
MfERG Ring 1 (At month-12)						
N1 amp. (nV/deg^2)	37.54±9.30	41.08±9.74	0.247*	36.50±8.31	41.52±10.25	0.088*
N1 imp. time (ms)	29.08±1.57	28.57±1.64	0.319*	29.18±1.49	28.56±1.68	0.212*
P1 amp. (nV/deg^2)	79.46±27.49	61.80±28.11	0.052*	83.77±24.96	60.59±28.21	**0.007***
P1 imp. time (ms)	49.66±0.85	49.64±0.73	0.938*	49.93±0.46	49.35±0.98	**0.022***
MfERG Ring 2 (Baseline)						
N1 amp. (nV/deg^2)	14.73±2.62	16.06±3.65	0.179*	15.39±2.81	15.06±3.42	0.736*
N1 imp. time (ms)	27.27±1.49	27.11±1.59	0.737*	27.32±1.56	27.10±1.50	0.647*
P1 amp. (nV/deg^2)	47.23±15.61	43.92±16.30	0.516*	48.20±16.26	43.51±15.21	0.341*
P1 imp. time (ms)	45.52±1.71	45.67±1.86	0.786*	45.56±1.68	45.59±1.86	0.955*
MfERG Ring 2 (At month-12)						
N1 amp. (nV/deg^2)	15.66±4.49	14.28±4.71	0.350*	16.99±2.88	13.17±5.32	**0.007***
N1 imp. time (ms)	27.08±0.99	26.75±1.12	0.323*	27.13±0.86	26.76±1.20	0.252*
P1 amp. (nV/deg^2)	41.43±9.40	37.54±7.31	0.166*	43.81±7.61	35.69±8.12	**0.002***
P1 imp. time (ms)	46.97±1.48	47.33±1.20	0.423*	46.97±1.41	47.25±1.36	0.521*

SD=Standard deviation, **MHD**=Minimum hole diameter, **BCVA**=Best-corrected visual acuity, **logMAR**=The logarithm of the minimum angle of resolution, **MI**= % macular integrity (0 - 40: Normal, 40 - 60: Suspect, 60 - 100: Abnormal), **AT**=Average threshold (36 - 25: Normal, 25 - 23: Suspect, 23 - 0: Abnormal), **dB**=Decibel. *Fix*, **Sta. P1**=% within 2 degree fixation (> 2/3: Stable, 1/3 - 2/3: Relative unstable, < 1/3: Unstable), *Fix. Sta.* **P2**=% within 4 degree fixation (> 2/3: Stable, 1/3 - 2/3: Relative unstable, < 1/3: Unstable), **MfERG**=Multifocal electroretinogram, **N1**=The first negative peak, **Amp**=Amplitude, **nV/deg^2**=Nanovoltage/area degree^2, **Imp. Time**=Latency. **Ms**=Milliseconds, **P1**=The first positive peak.
*Independent-Samples t test.

DISCUSSION

The ILM is formed by the footplates of the Müller cells, which play a critical role in the development and physiologic functioning of the retina. Hence, the ILM acts as a scaffold for cellular integrity and proliferation (Almony A et al., 2012). Even if no surgical complications occur, removal of the ILM can result in anatomic changes in the retina, such as a DONFL appearance (Ito Y et al., 2005; Tadayoni R et al., 2001). Also, recent evidence has shown that ILM peeling may cause widespread trauma to the ganglion cell and retinal nerve fiber stratums, which corresponds to inner retinal dimpling on cross-sectional OCT images (Avci R, Mavi Yildiz A & Yilmaz S, 2021).

It has been speculated that N1 is originated from photoreceptors in the external retinal stratum and that P1 is originated from bipolar and Müller cells (Graham SL & Klistorner A, 1998). The amplitudes were shown to change widely, even in patients with equal grades of visual acuity. However, after surgery, amelioration in mfERG amplitudes was reported even with unchanged visual acuity according to baseline values (Moschos M et al., 2001; Si YJ, Kishi S & Aoyagi K, 1999). If external retinal stratums are intact after surgery, the function of photoreceptors will presumably improve, N1 value will presumably increase, and it will also be followed by the recovery of the inner retinal layers, which is represented by the P1 value. Nevertheless, this is not always the case because removing the ILM may negatively affect these inner stratums. In this study, the postoperative mean P1 amplitude increased compared with the preoperative values of mfERG in ring 1. Following the surgery, the recovery in retinal response density in mfERG ring 1 appeared to be the result of the hole closure with a realignment of the photoreceptor layer and glial cell activation. However, the postoperative mean P1 amplitudes decreased compared with the preoperative values in mfERG in other rings. The rings were related to the area of ILM peeling. Following the surgery, a worsening of the retinal response density in mfERG in the same rings may be a result of ILM peeling and reduced activity of Müller cells. Moreover, after surgery, the implicit time of N1 and especially P1 were delayed in the same rings. In general, delayed implicit time in mfERG is detected in ischemic pathologies of the macula such as diabetes and vein occlusion (Abdel-Kader M & El-Dessouky MW, 2010).

The delay may be related to surgical trauma or even ischemia in the ILM peeling area.

The outcomes of microperimetry are controversial: some researchers found no changes after peeling, whereas others detected new-onset microscotomas (Imai H & Ohta K, 2010; Mitamura Y & Ohtsuka K, 2005). In this study, improvements of MI, AT, and fixation stability P1 values were found compared with baseline measurements. However, regarding the retinal sensitivity of the 37 points, there was a reduction of 22.1% in the ILM peeling area. Also, absolute paracentral microscotomas were detected in two points of two eyes at month 12. Tadayoni et al. stated that absolute paracentral microscotomas could occur after ILM peeling (Tadayoni R et al., 2012). Retinal susceptibility worsening and microscotomas may be due to impairment of the retina, particularly of the Müller cells, the foot processes of which are closely related to the ILM and may be affected by ILM peeling. Impairment of other retinal cells is also conceivable, either directly, due to the trauma caused by ILM peeling, or indirectly, due to Müller cell impairment. This deterioration may appear as absolute scotoma, as in this study.

The BCVA level depends on the sensitivity of the center of the fovea. The median BCVA in the patients in the present study ameliorated after surgery. Also, regression analysis showed that the minimum hole diameter was the only reliable predictor for the BCVA at month 12. Visual acuity improves in almost all patients after macular hole surgery. However, in these patients, vision gain is not the only problem. Metamorphopsia should also be assessed postoperatively in patients with a macular hole. This study showed that metamorphopsia could occur in nearly half of patients at 12 months after surgery. Sigura et al. reported that the mean scores of postoperative metamorphopsia were significantly correlated with preoperative base hole diameter (Sugiura Y et, 2017). However, Wada et al. announced no significant correlations between metamorphopsia scores and baseline OCT data (Wada I et al., 2017). Binary logistic regression analysis showed that symptoms of metamorphopsia were only associated with EZ defects at month 12 in this study. Preoperative minimum hole diameter, MP, and mfERG parameters were not associated with metamorphopsia. Recent theories emphasized that metamorphopsia could be sourced by the displacement of retinal stratums leading to mislocation of light on the retina after macular hole surgery (Wiecek E et al., 2014). In a previous study, our group reported that foveal displacement might be one of the major contributing factors for postoperative metamorphopsia in addition to EZ disruption (Yilmaz S, Yildiz Mavi A & Avci R, 2021). The potential limitations of this research include the retrospective and non-comparative design, and manual measurements of SD-OCT parameters. Another limitation was the lack of use of M-CHART to quantify the degree of metamorphopsia. However, this study reveals valuable data regarding the possible negative effect of ILM peeling on MP and mfERG parameters after macular hole surgery.

CONCLUSION

ILM peeling may cause a reduction in retinal susceptibility and electrical potential in addition to postoperative microscotomas. In the light of these results, it may be suggested that peeling of the ILM should be avoided in cases with an unclear potential benefit. However, if peeling is decided on, the surface that is peeled should be restricted to the bare minimum.

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Conflict of Interest
The author declares that he has no conflict of interest.

Author Contributions
SY performed the data collection, planning, and analysis, drafted the manuscript, and designed the tables and figures.

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