Preservation of the Photoreceptor Layer Following Subthreshold Laser Treatment for Diabetic Macular Edema as Demonstrated by SD-OCT

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Purpose. Subthreshold laser treatment of diabetic macular edema (DME) may have less deleterious effects on the photoreceptors than regular continuous wave laser. This study aimed to assess whether subthreshold laser causes a long-term damage to the retinal structures, as demonstrated by spectral-domain optical coherence tomography (SD-OCT), and to evaluate the change in the axial diameter of retinal diabetic microaneurysms following treatment.

Methods. A retrospective study of eyes that were diagnosed with nonfoveal involving DME and underwent subthreshold laser treatment with the Novus SRT system. Spectral-domain OCT scans of treated retinal areas, performed prior to treatment and approximately 4 months following treatment, were assessed for changes in the continuity of the photoreceptor (PR) layer, the thickness of the PR-RPE layer, the retinal thickness at the treatment sites, and the diameter of the microaneurysms.

Results. Included in this study were 31 microaneurysms. Following treatment, the continuity of the ellipsoid zone of the inner segments of the photoreceptors was confirmed in all but two cases. The thickness of the PR-RPE layers was 72.32 ± 7.36 and 70.97 ± 7.27 μm prior to and following treatment, respectively ($P = 0.061$). The retinal thickness at the treatment sites decreased from 398.65 ± 57.89 to 372.74 ± 60.4 μm ($P < 0.001$). The mean measured diameter of the microaneurysms was 87.32 ± 27.45 and 6.68 ± 26.12 μm, respectively ($P < 0.001$).

Conclusions. In this study, subthreshold laser treatment for DME has been shown to be a safe technology that preserves the photoreceptor layer, as demonstrated by SD-OCT.

Keywords: optical coherence tomography, subthreshold laser treatmsent, photoreceptors, retinal pigment epithelium, microaneurysms

Traditionally, the treatment of diabetic macular edema (DME) was based on the application of direct continuous wave thermal laser to leaking retinal microaneurysms or areas of retinal thickening (i.e., focal-direct or grid-laser treatment).[1] This was the only proven treatment modality for years, until the recent advent of the efficacious pharmacological treatment for DME. A large scale study has shown that thermal laser treatment may still have a role in the treatment of DME as an adjunct to pharmacological therapy.[2]

Subthreshold laser treatment of the retina is another technique based on a sequence of laser pulses, whose duration is shorter than the relaxation time of the RPE cells. The result is that the thermal energy delivered is confined mostly to the RPE cells, with minimal and reversible collateral damage to the adjacent retinal structures, such as the outer segments (OS) of the photoreceptors (PR).[3] This form of treatment has been efficacious in treating DME in small pilot clinical trials.[4,5] Prior studies had not described spectral-domain optical coherence tomography (SD-OCT) findings of the microaneurysms, PR, and the RPE in retinal areas treated with subthreshold laser.

The primary objective of this study was to examine whether subthreshold focal laser treatment of DME induces a change in the outer retinal layers, as demonstrated by SD-OCT.

The secondary objectives were to assess changes in retinal thickness at the treatment site; the thickness of the outer retinal layers including the RPE and the PR; and demonstrate any change in the measured axial diameter of the microaneurysms following treatment.

Methods

This retrospective case study was approved by the Tel Aviv Medical Center ethics committee and followed the tenets of the Declaration of Helsinki. All enrolled patients had been diagnosed with DME without foveal involvement. These patients were subjects of another clinical study that assessed the efficacy of subthreshold laser therapy in reducing the risk of DME progression into the center of the fovea.

Eyes included in that study were treated with subthreshold laser with the Novus selective retinal therapy (SRT) system (Lumenis Ltd., San Jose, CA, USA). The treatment was performed in a grid pattern on areas of thickened retina, as proven by SD-OCT. This was a Q-switched frequency-doubled neodymium-doped yttrium lithium fluoride–pulsed laser device with a wavelength of 527 nm. The spot size was fixed at 200 μm. The laser generated 1.7-μs laser pulses at a repetition rate

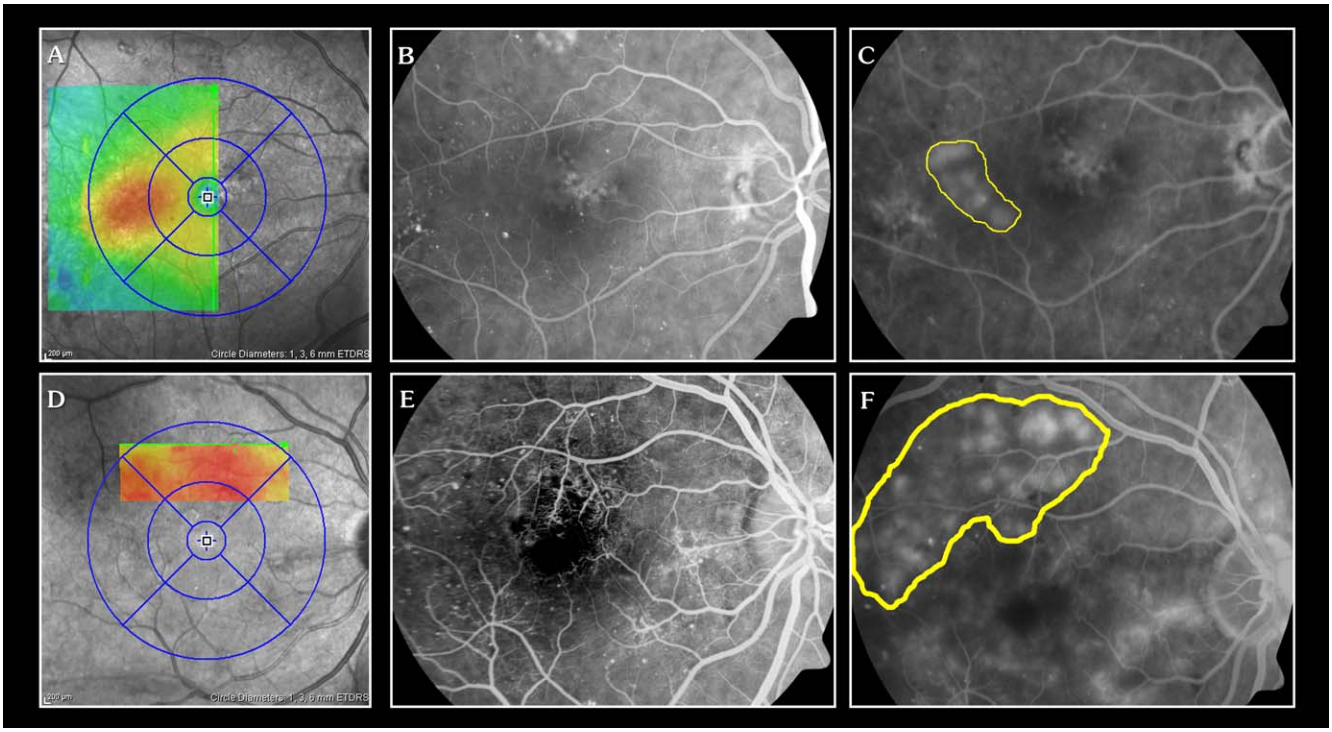

FIGURE 1. Panels (**A**–**C**) correspond to case #12, while (**D**–**F**) correspond to case #10. (**A**, **D**) Optical coherence tomography thickness maps depicting the thickened retinal areas. (**B**, **E**) Pretreatment FA images depicting the microaneurysms. (**C**, **F**) Fluorescein angiography images taken 2 hours following subthreshold laser treatment. The treated retinal areas are encircled with *yellow lines*.

of 100 Hz. A treatment shot consisted of a sequence of 30 pulses, each of 1.7 μs in duration, with a 10-ms rest period in between each pulse. Therefore, the total exposure duration was 300 ms. These short-duration pulses confine the heating to the RPE cells, sparing the adjacent PR cells from damage. The energy per pulse was titrated from 50 to 500 μJ in each patient. All treatment sessions commenced with test shots performed near the temporal vascular arcades. The laser power was titrated until it resulted in a lightly visible burn; then power was reduced by 30% in order to treat the thickened areas, including the microaneurysms, with subthreshold laser energy.

The abovementioned study's inclusion criteria required a central macular field thickness of 315 μm or less (as measured by the Heidelberg Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany), and that the retinal subfield treated with the laser would be of at least 350 μm in thickness. The treated microaneurysms were all extrafoveal. Only one eye from each patient was included in the study.

All patients underwent a complete ophthalmic evaluation. The diagnosis of DME was confirmed by fluorescein angiography (FA) and SD-OCT, which were performed prior to treatment. Only retinal areas with microaneurysms that demonstrated leakage prior to treatment were included in the current study. Since subthreshold laser burns can only be identified by angiography, all included eyes had an additional FA performed promptly after treatment in order to confirm that the treatment was conducted and detected in the selected areas. These images were used to illustrate the treated retinal areas (Fig. 1). Angiography data was also available during the follow-up period.

The patients were examined and followed-up with Heidelberg Spectralis SD-OCT every 4 months. The current study's inclusion criteria required the existence of SD-OCT scans depicting the treated microaneurysms in their specific retinal locations (as described elsewhere[6,7]) prior to laser treatment and at least 4 months following treatment. These microaneurysms were used as markers of retinal locations. In order to facilitate the localization of the microaneurysms on SD-OCT, the infrared OCT scans, and the FA images were juxtaposed and compared. The SD-OCT images of the corresponding locations of the angiographically proven treatment sites were examined for the typical appearance of diabetic microaneurysms. If the treated microaneurysms were not imaged by OCT prior to treatment, they were excluded from analysis. The prominent OCT layer corresponding with the ellipsoid zone (EZ) of the inner segments (IS) of the PR, that was previously attributed to the boundary between the IS/OS of the PR was examined as well and defined as either continuous, discontinuous, or absent.[8] Included cases were required to have continuous EZ prior to treatment. It should be noted that this paper uses the term IS/OS instead of EZ when referencing previous studies for purposes of consistency.

In order to facilitate the precise detection of the same retinal locations (i.e., sites of the microaneurysms) in posttreatment OCT scans, the Heidelberg Spectralis SD-OCT follow-up tracking protocol was used. This module provides better precision in rescanning a specific retinal site whose location was marked in the original baseline scan. Therefore, only eyes scanned with this follow-up tracking protocol were included in the current study. To clarify, see Figure 1D: there are two green marker lines. A green arrow is directed nasally in that image, this arrow marks the plane of the OCT scan. A smaller dashed line is perpendicular to this arrow, this line marks a specific location on that plane, and can be placed on a specific site depicting a microaneurysm. The point where these two lines meet marks a particular retinal location. The boundaries of the OCT scanned area are portrayed by the rectangle filled with red whose top edge coincides with the green arrow. The follow-up tracking system allows the same retinal areas to be scanned in the same transverse density if

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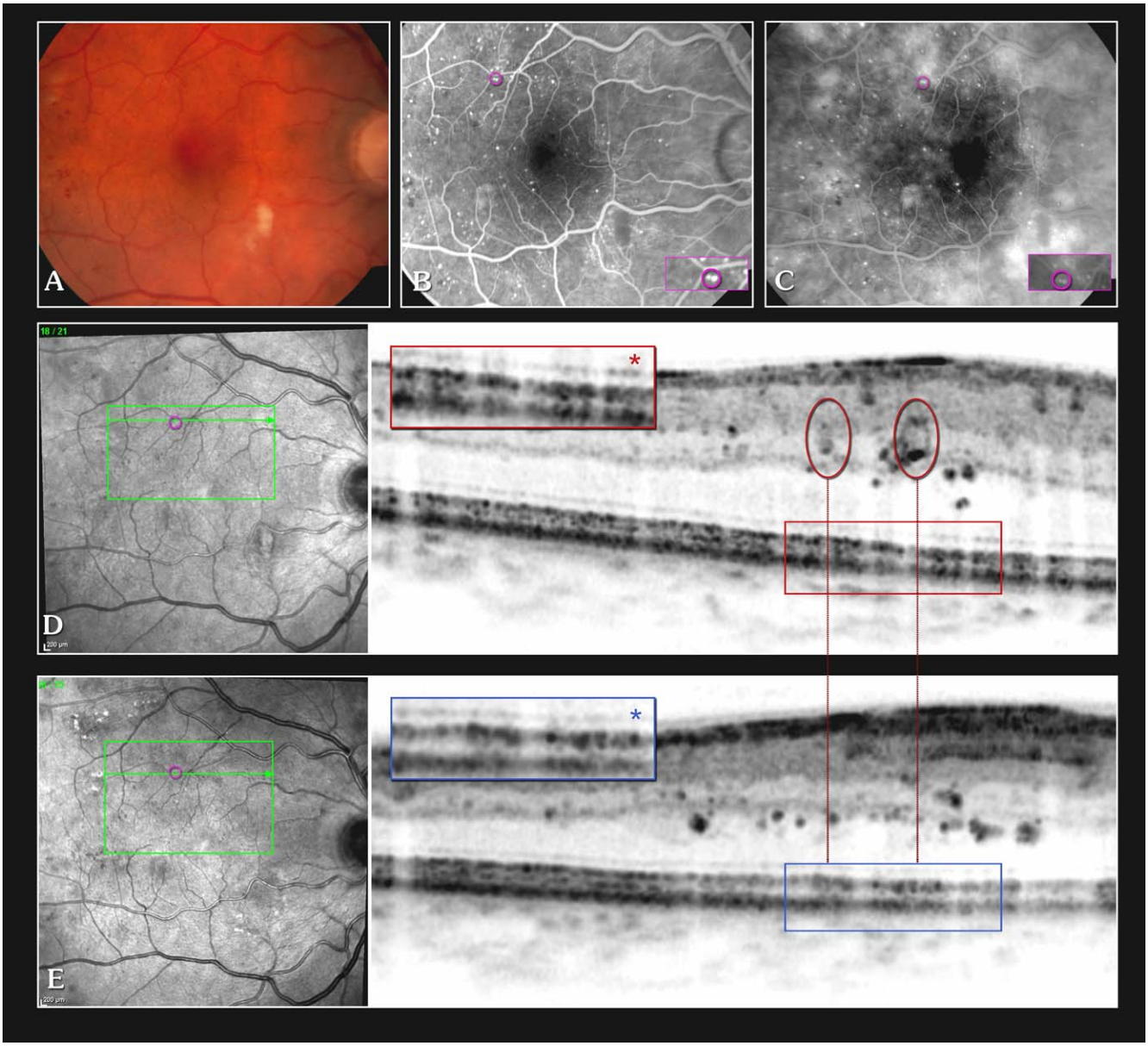

FIGURE 2. (**A**) A color fundus photograph of the right eye of one of the study's participants. (**B**) Fluorescein angiography performed 2 hours following subthreshold laser treatment in the same eye. The studied microaneurysms are circled in *purple* in this early phase image. A high-magnification image of the studied microaneurysm and their relation to the blood vessels is shown in the *lower right*. (**C**) A late-phase image from the same FA study. The studied microaneurysms are circled in *purple* in this image, and are also shown in high magnification in the *lower right*. (**D**) Pretreatment: an infrared scan on the *left side* of the panel, and an SD-OCT scan on the *right*. The studied microaneurysms are circled in *purple*. The PR-RPE layers are depicted within the *red rectangle*. The *asterisked rectangle* is a magnification. (**E**) Four months posttreatment: the *vertical lines* mark the former locations of the microaneurysms, which are now undetectable. The PR-RPE layers are within the *blue rectangle*, and the *asterisk* marks a magnified view.

they were predefined in the first scans. Corresponding OCT images performed at the same plane were assessed in posttreatment OCT images without moving the dashed marker, therefore all posttreatment evaluations were performed in the exact retinal location set at baseline where a microaneurysm was demonstrated. All imaged microaneurysms in every eye that fulfilled the requirements were included in our study.

The thickness of different structures within the retina was measured using the Heidelberg Spectralis built-in caliper module and was performed by one skilled ophthalmologist specializing in ocular imaging (DG). All images were magnified using the built-in magnifier module and the contrast was adjusted in order to delineate the borders of different retinal structures. The main study's parameters included the retinal thickness at the site of the microaneurysms, the presence of EZ defects (as defined above), and the thickness of the PR-RPE layer. This was performed prior to and following treatment. The measurements were performed at the same retinal sites for both pre- and posttreatment scans, as described above. The retinal thickness at the site of the microaneurysms was the axial distance measured between the internal limiting membrane and Bruch's membrane. Bruch's membrane correlated with the fourth anteroposterior band of the outer retina, as defined by Spade et al.[8] The thickness of the PR-RPE layer was assessed by measuring the vertical length of the layer posterior to the microaneurysms and encroached between the external

Table 1. Demographic Data

Patient #	Sex	Age, y	Follow-up, d
1	Male	52	139
2	Male	52	136
3	Female	53	120
4	Male	63	125
5	Male	51	125
6	Male	74	132
7	Male	56	137
8	Male	53	119
9	Female	73	120
10	Male	55	120
11	Female	55	117
12	Male	65	120
13	Female	79	116
14	Female	60	136
15	Female	75	116
16	Male	58	119
17	Female	63	117
18	Female	62	138
19	Male	58	160
Mean		60.89	126.95
SD		8.70	11.58

limiting membrane and Bruch's membrane (i.e., the first and fourth bands as defined by Spade et al.[8]). In addition, the OCT scans were evaluated for the largest demonstrable microaneurysmal anteroposterior (axial) diameter in the available scans of each specific microaneurysm. The walls of the microaneurysms were depicted as hyperreflective signals on the Heidelberg Spectralis OCT, as demonstrated in Figure 2D. The measurement of the microaneurysmal diameter was defined as the axial distance between the anterior and posterior hyperreflective dots (marking the anterior and posterior poles of the microaneurysms). For each identified microaneurysm, adjacent horizontal scans were also examined, and the largest measured diameter was noted as the microaneurysm measured diameter. This reading was referred to as microaneurysm diameter in this manuscript. These measurements were performed both before and following treatment and at the same retinal location, as described above. After treatment, the diameter of the microaneurysm was set at 0 in cases where a follow-up OCT scan that passed exactly at the site of a pretreatment demonstrated microaneurysm did not reveal a microaneurysm-like structure. Adjacent scans were carefully examined as well to verify the disappearance of the microaneurysm following treatment.

Central macular thickness (CMT) was assessed using the Heidelberg Spectralis module for thickness map.

Statistical Analysis

The statistical analysis was performed using an SPSS software version 15.0 (SPSS, Inc., Chicago, IL, USA). Parametric variables were analyzed using a paired *t*-test. Nonparametric variables were analyzed using a McNemar test. Correlations were performed with the Pearson test.

Results

This study included 19 eyes of 19 patients: eight right eyes and 11 left eyes of 11 males and eight females were included in the study. Fifteen other patients were excluded because their OCT scans did not depict any microaneurysms: a total of 168 microanuerysms were detected by FA prior to treatment, however only 31 of them were also depicted by OCT. This resulted in a total of 31 cases of eligible microaneurysms. All patients had type 2 diabetes mellitus. The mean age at treatment was 60.89 ± 8.7 years (mean ± SD). The mean follow-up period was 126.95 ± 11.58 days (median, 120 days). See Table 1 for the demographic data.

The posttreatment continuity of the EZ was assessed. In two cases alone, the EZ layer was discontinuous. In all other cases (29 of 31), it was continuous and preserved without a significant change in comparison to baseline (McNemar test: $P = 0.5$). In none of the cases was the layer absent. See Table 2 for a detailed description of the OCT parameters.

The thickness of the PR-RPE layer was 72.32 ± 7.36 μm prior to treatment, and 70.97 ± 7.27 μm following treatment ($P = 0.061$). The median thickness remained unchanged at 71 μm. In six cases, the layer was thicker than baseline. In another 14 cases, it remained unchanged.

The pretreatment mean axial diameter of the microaneurysms was 87.32 ± 27.45 μm (Fig. 2). The overall mean diameter after treatment was 6.68 ± 26.12 μm ($P < 0.001$). In all but two cases, the microaneurysms were entirely obliterated and invisible after treatment. In one case, the microaneurysm's diameter remained unchanged, although treatment was confirmed by FA. In another case, the microaneurysm's diameter was reduced after treatment, but not completely obliterated. No significant correlations were found between the study's above mentioned OCT parameters, including: retinal thickness at the site of the microaneurysms, axial diameter of the microaneurysms, thickness of the PR-RPE layer, as well as age.

The mean pretreatment retinal thickness at the site of the microaneurysms was 398.65 ± 57.89 μm. It decreased to 372.74 ± 60.4 μm following treatment ($P < 0.001$). Although in most cases examined the retinal thickness was reduced following the application of laser, it remained unchanged in two sites, and was increased in four.

The mean central macular thickness was 285.58 ± 19.2 μm prior to treatment, and 280.58 ± 31.36 μm after treatment (P = NS).

Discussion

This study's findings have shown that subthreshold laser treatment performed with the Lumenis Novus SRT system is effective in preserving the continuity of the EZ layer on SD-OCT. A very mild reduction (1–2 μm on average) was observed in the thickness of the PR-RPE layer after treatment. The mean retinal thickness at the treatment sites was reduced compared with baseline, and most of the microaneurysms included in this study were found to be obliterated in the posttreatment scans.

A preclinical study performed in animals has shown that the majority of the neurosensory retina may be spared by targeting the RPE with repetitive, low energy, microsecond laser pulses that are shorter in duration than the thermal relaxation time of the RPE.[3] On the other hand, a continuous wave laser burn (which is similar to the traditional widespread laser treatment) with an exposure time of as little as 50 ms resulted in damage to adjacent retinal structures. Scanning electron microscopy images of eyes treated with the subthreshold laser demonstrated that the RPE defect was filled up with spreading and migrating RPE cells originating from the surrounding RPE. However, the animal study did not demonstrate in vivo preservation of the PR after subthreshold laser treatment.

A subsequent human pilot study showed that retinal burns created by up to 100 micropulses may be undetected by microperimetry, suggesting in vivo preservation of the IS/OS of the PR after exposure to such photocoagulation technique.[9]

Table 2. OCT Data

Patient #	Microaneurysm #	# Pre-FA	# OCT	CMT-pre	CMT-post	Preretinal Thickness	Postretinal Thickness	Pre–PR-RPE Thickness	Post–PR-RPE Thickness	Pre-diameter	Post-diameter	PR-post
1	1	6	1	291	375	361	343	69	61	69	0	1
2	2	8	2	268	275	378	358	73	73	81	0	1
	3					431	391	81	81	70	0	1
3	4	13	2	295	282	365	340	72	72	96	0	1
	5					355	309	64	70	70	0	1
4	6	9	1	296	292	346	326	69	69	118	118	2
5	7	8	2	295	298	372	362	65	69	72	0	1
	8					348	348	66	69	45	0	1
6	9	4	1	298	293	368	337	71	71	69	0	1
7	10	6	2	263	253	427	327	65	58	83	0	2
	11					299	289	79	72	65	0	1
8	12	4	1	312	308	428	416	72	72	148	0	1
9	13	4	1	303	298	335	363	74	74	64	0	1
10	14	11	2	300	288	410	375	69	69	55	0	1
	15					465	416	83	76	68	0	1
11	16	9	1	281	288	335	335	76	70	62	0	1
12	17	9	2	251	245	374	301	59	59	118	0	1
	18					354	305	67	65	61	0	1
13	19	6	1	249	242	507	459	87	87	124	0	1
14	20	11	2	299	248	412	406	64	66	85	0	1
	21					433	439	67	73	92	0	1
15	22	12	2	263	261	434	385	86	80	75	0	1
	23					431	364	83	84	124	0	1
16	24	15	2	311	296	461	413	79	76	103	0	1
	25					368	341	83	83	72	0	1
17	26	13	2	296	239	299	279	62	59	83	0	1
	27					527	417	76	72	117	0	1
18	28	12	2	276	277	365	365	72	72	76	0	1
	29					413	416	69	69	158	89	1
19	30	8	2	279	273	473	462	69	60	106	0	1
	31					484	568	71	69	78	0	1
Mean				285.58	280.58	398.65	372.74	72.32	70.97	87.32	6.68	
SD				19.20	31.36	57.89	60.40	7.36	7.27	27.45	26.12	

Patient #, the serial number of the study's participants; Microaneurysm #, the serial number of the microaneurysm included in the study. All measurements are in micrometers (excluding the assessment of the continuity of the PR layer); # Pre-FA, the number of microaneurysms that were identified on fluorescein angiography in the area scanned by OCT prior to treatment; # OCT, the number of microaneurysms that were identified on OCT and included in the study; CMT-pre, central macular thickness prior treatment; CMT-post, central macular thickness following treatment; Preretinal thickness, retinal thickness at the site of the microaneurysm prior to treatment; Postretinal thickness, retinal thickness at the site of the microaneurysm following treatment; Pre–PR-RPE thickness, thickness of the PR-RPE layer prior to treatment; Post–PR-RPE thickness, thickness of the PR-RPE layer following treatment; Prediameter, diameter of the microaneurysm prior to treatment; Postdiameter, diameter of the microaneurysm following treatment; PR-post, continuity of the PR layer following treatment (1, continuous IS/OS; 2, discontinuous).

While providing functional evidence, that study did not provide in vivo imaging of the PR at the treated sites.

An additional human pilot study showed that this method of subthreshold photocoagulation may lead to favorable outcome measures, such as the preservation of visual acuity and the reduction in angiographic and clinical exudation in treated eyes with DME and central serous retinopathy.[4] The study did not provide OCT data.

Another small human study in eyes with DME demonstrated a mild improvement in best corrected visual acuity after a follow-up period of 6 months.[5] A mean reduction of 12 μm in central retinal thickness demonstrated by OCT was also noted, but the measurement was not statistically significant. The OCT system used in that study was the Stratus OCT-3, while in the current study a SD-OCT was used, and thus the images were of a higher axial resolution. The clearer images facilitated the identification of microaneurysms. Also, structures such as the RPE and the EZ were demonstrated more precisely.

An additional study that dealt with the treatment of DME with micropulsed laser, compared with traditional continuous wave laser, showed similar results.[10] After 1 year of follow-up, the group treated with high-density subthreshold diode-laser micropulse photocoagulation had better results in terms of an improvement in best-corrected visual acuity and central macular thickness than eyes treated with focal/grid laser photocoagulation or normal density subthreshold diode laser photocoagulation. That study, which used a micropulse laser system, did not provide SD-OCT structural information on the retinal sites treated. In the current study, all but two microaneurysms were shown to be obliterated following subthreshold laser treatment. The retinal thickness at the site of treatment was significantly reduced by a mean of approximately 26 μm. The central macular thickness, however, was not significantly reduced following treatment. This may reflect the baseline characteristics of the patients, who did not have central involving macular edema (pretreatment CMT was required to be lower than 315 μm).

Several studies have described morphologic findings in the retinal layers following laser treatment using SD-OCT. A study of DME that focused on the retinal changes observed 1 day following grid continuous wave laser photocoagulation revealed that the RPE layer was attenuated in those eyes. Damage

was also observed in the PR layer and, to a lesser extent, in the outer nuclear layer.[11] A different study of the same group revealed that 3 months following treatment, the laser-induced changes were confined to the lower PR level.[12] Cyst formation and diffuse swelling in the inner and outer nuclear layers were still detectable to some extent. Approximately 2 months following treatment, the IS/OS and external limiting membrane became continuous again. This was observed in 55% of the lesions examined. In the remainder of the cases, a hyperreflective deposit was imaged on the level of the RPE, with a secondary interruption of the IS/OS. The external limiting membrane's continuity was restored in all cases. In the current study, the EZ continuity was observed in all but two cases (compared with 55% in the abovementioned study).

A study of eyes treated with grid laser photocoagulation for DME, scanned with polarization sensitive OCT, showed also that the RPE was damaged by laser energy, and that the RPE responded in typical healing patterns.[13] The current study did not use such a method to assess the RPE, but using standard SD-OCT, the mean thickness of the PR-RPE layer was virtually unchanged. Another study that used threshold energy, and then produced laser burns with half that energy (reduced fluence), showed that both types of lesions have similar characteristics.[14] However, the damage to the PR-RPE and the adjacent retinal structures was reduced in the reduced fluence group, and there was a tendency for IS/OS reorganization. These results suggest that even reduced fluence continuous wave laser is harmful to the RPE, which is contradictory to the findings of the current study, in which subthreshold laser was used. Another study of eyes treated with subvisible diode micropulse laser for DME, which used an SD-OCT system for the detection of morphologic changes, noted that the laser treatment had not resulted in focal disruption, discontinuity or scarring of any retinal layers after a median follow-up of 12 months.[15] These results are consistent with the results of the current study, which has also demonstrated the continuity of the EZ layer following subthreshold laser treatment, in all but two cases (2 of 31).

The current study has provided SD-OCT evidence for the continuity of the IS/OS of the PR in the majority of treated targets imaged by OCT suggesting minimal or no damage to the EZ of the PR. There was a small, nonsignificant reduction in the thickness of the RPE and PR layers. This reduction may be attributed to the relative RPE defect caused by the application of laser energy.[9] The study results have also suggested that subthreshold laser treatment performed in grid fashion may be effective in obliterating microaneurysms. This was not demonstrated in prior studies.

A notable shortcoming of this study is its retrospective nature: it relied on existing OCT data. In most cases, the OCT scans were widely spaced (120–240 μm), and resulted in a relatively low number of identifiable microaneurysms on OCT. This low yield is contrasted by the high number of microaneurysms detected by pretreatment FA (Table 2). Still, the final study group consisted of a total of 31 microaneurysms, which was sufficient for statistical analysis.

Traditional macular laser treatment with continuous wave laser induces an RPE scar that extends to the PR layer, inducing a scotoma at the treatment site. Subthreshold laser treatment is designed to deliver energy to the RPE alone, without causing detrimental changes in the overlying PR layer. In the cases included in this study, the continuity of the EZ and the thickness of the PR-RPE layer were preserved following treatment. This provides additional in vivo data on the safety of this treatment modality.

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