# MICROPERIMETRY AND FUNDUS AUTOFLUORESCENCE IN DIABETIC MACULAR EDEMA

## Subthreshold Micropulse Diode Laser Versus Modified Early Treatment Diabetic Retinopathy Study Laser Photocoagulation

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**Purpose:** The purpose of this study was to evaluate and compare microperimetry and fundus autofluorescence (FAF) after subthreshold micropulse diode laser versus modified Early Treatment Diabetic Retinopathy Study photocoagulation for clinically significant diabetic macular edema.

**Methods:** A prospective randomized clinical trial including 62 eyes (50 patients) with untreated, center-involving, clinically significant diabetic macular edema was performed. All patients underwent best-corrected visual acuity determination (logarithm of the minimum angle of resolution), slit-lamp biomicroscopy, FAF, optical coherence tomography, microperimetry (macular sensitivity), and fluorescein angiography before and after treatment. Best-corrected visual acuity, optical coherence tomography, microperimetry, and FAF were repeated at 1-, 3-, 6-, 9-, and 12-month follow-up examinations. Fluorescein angiography was performed at baseline and at 6 and 12 months.

**Results:** Before treatment, demographic and macular parameters were not different between the two treatment groups. At 12 months, best-corrected visual acuity remained stable in both groups ($P = 0.41$ and $P = 0.82$), mean central retinal thickness decreased in both groups ($P = 0.0002$ and $P < 0.0001$), and mean central 4° and 12° retinal sensitivity increased in the micropulse diode laser group ($P = 0.02$ and $P = 0.0075$) and decreased in the Early Treatment Diabetic Retinopathy Study group ($P = 0.2$ and $P = 0.0026$). There was no significant difference in either best-corrected visual acuity or central retinal thickness between the 2 treatment groups ($P = 0.48$ and $P = 0.29$), whereas there was a significant difference in 4° and 12° retinal sensitivity ($P = 0.04$ and $P < 0.0001$). Fundus autofluorescence never changed in the micropulse diode laser group even after retreatment. In the Early Treatment Diabetic Retinopathy Study group, FAF increased up to 9 months and decreased in 6 eyes (20%) at 12 months.

**Discussion:** Micropulse diode laser seems to be as effective as modified Early Treatment Diabetic Retinopathy Study laser photocoagulation in the treatment of clinically significant diabetic macular edema. Micropulse diode laser treatment does not determine any change on FAF showing (at least) nonclinically visible damage of the retinal pigment epithelium. Microperimetry data encourage the use of a new, less aggressive laser therapeutic approach in the treatment of clinically significant diabetic macular edema.

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Macular edema is the main cause of visual loss in patients with diabetes.[1] The gold standard treatment for clinically significant diabetic macular edema (CSME) is visible endpoint argon laser photocoagulation proposed by the Early Treatment Diabetic Retinopathy Study (ETDRS).[2] This treatment proved to be an effective method in decreasing the risk of moderate visual loss in patients with CSME.[2] However, the

beneficial effect of conventional laser photocoagulation is associated with severe destruction of retinal photoreceptors, progressive enlargement of laser retinal scars (up to foveal atrophy), and development of choroidal neovascularization and subfoveal fibrosis.[3–6] Moreover, despite the proven benefit in the stabilization of visual acuity, laser photocoagulation for CSME invariably results in a localized loss of perimetric sensitivity within 10° eccentricity of the fovea.[3,7]

Recently, many investigators have tried to use less aggressive treatment strategies, using barely visible or invisible (subthreshold) laser spots, to obtain the resolution of CSME.[8–10] ''Light'' and ''mild'' macular laser photocoagulation has shown results comparable to the modified ETDRS protocol.[8,9,11] Subthreshold micropulse laser treatment, using a 810-nm diode laser (micropulse diode laser [MPDL]), has been shown to be effective in the treatment of CSME in terms of best-corrected visual acuity (BCVA), retinal thickness (optical coherence tomography [OCT]), and contrast sensitivity.[12] The difference between MPDL and modified ETDRS treatment is that the ETDRS treatment group has a higher risk of developing laser scars.[12]

The principal aim of this study was to determine and compare short- and midterm retinal sensitivity (RS) and fundus autofluorescence (FAF) changes after subthreshold MPDL treatment versus modified ETDRS laser photocoagulation in eyes with center-involving CSME. The secondary aim of this study was to determine and compare BCVA and OCT changes after both treatments.

## Materials and Methods

A prospective, masked, randomized clinical trial including 62 eyes (50 patients) with untreated CSME was performed. All patients were recruited from the Diabetic Retinopathy Clinic at the Department of Ophthalmology, University of Padova, from 2005 to 2007.

The inclusion criteria were men or women with type 2 diabetes mellitus and an HbAlC $\leq$10%; previously untreated CSME involving the center of the macula, defined according to the ETDRS protocol on stereo fundus photography[13]; and foveal thickening of at least 250 $\mu$m confirmed with OCT and BCVA of at least 35 letters on the modified ETDRS chart (logarithm of the minimum angle of resolution [logMAR 1.0]).

The exclusion criteria were any type of previous macular treatment (macular laser photocoagulation, vitrectomy, intravitreal steroids, and/or antiangiogenic drugs), any intraocular surgery at least 6 months before the treatment, ischemic maculopathy, tractional maculopathy, and significant media opacities that precluded fundus examination or imaging.

Written informed consent was obtained from all patients, and approval for this study was obtained from our institutional ethics committee. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

All patients underwent BCVA determination (logMAR), slit-lamp biomicroscopy, FAF, fluorescein angiography, OCT, and microperimetry (macular sensitivity) before and after treatment. Patients randomly underwent subthreshold MPDL treatment versus modified ETDRS green laser photocoagulation. In case of CSME presence in both eyes, the right eye was randomly selected for one treatment, and the left eye received the opposite treatment. Best-corrected visual acuity, OCT, microperimetry, and FAF were repeated at the 1-, 3-, 6-, 9-, and 12-month follow-up examinations. Fluorescein angiography was performed at baseline and at 6 and 12 months.

### *Study Procedures*

*Visual acuity.* Best-corrected visual acuity for each eye was measured by a certified tester using the standard ETDRS protocol at a distance of 4 m with a modified ETDRS distance chart transilluminated with a chart illuminator (Precision Vision, Bloomington, IL).[14] Visual acuity was scored as the total number of letters read correctly and expressed in logMAR.

*Fundus autofluorescence.* Fundus autofluorescence was recorded with a confocal scanning laser ophthalmoscope (Heidelberg retinal angiograph, HRA 2, Heidelberg Engineering, Heidelberg, Germany) using the argon blue wavelength (488 nm). The optical and technical principles of the Heidelberg retinal angiograph have been previously described in detail.[15,16] To amplify the autofluorescence signal of the final image, 10 acquired images were aligned, and a mean image was calculated from these after detection and correction of eye movements were performed by image analysis software. Digital images were saved on a hard disk for further analysis and processing. Fundus autofluorescence images were graded for different patterns (normal, increased, and decreased) before and after treatment.[17]

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*Stereo fundus photography and fluorescein angiography.* Color stereoscopic fundus photographs and fluorescein angiography of the ETDRS field 2 were taken in all patients after an adequate dilatation by a certified photographer using the same TOPCON TRC 50IA 35° fundus camera (Topcon, Tokyo, Japan) and were saved in JPEG format.[18] Two retinal specialists independently graded each pair of images on a 17-inch monitor dedicated to diabetic retinopathy screening. Center-involving CSME was graded according to the ETDRS protocol.[18] Fluorescein angiography images were graded for capillary loss and the presence and extent of fluorescein leakage.

*Optical coherence tomography.* Optical coherence tomography scanning was performed on a Stratus OCT TM scanner (Carl Zeiss Meditec, Inc., Dublin, CA) with the 4.1 (0.052) version software. The scanning protocol used for this study was a ''fast macular thickness'' program, which creates a retinal map algorithm consisting of 6 radiating cross-sectional scans, each with a length of 6 mm, that produce a circular plot in which the foveal zone is the central circular zone with a 1.00-mm diameter. For the purpose of this study, retinal thickness in the central 1 mm was used as the OCT measurement of foveal thickness. Only eyes with a mean central thickness $\geq$250 $\mu$m were included in this study.

*Microperimetry.* Microperimetry was performed on all subjects using the MP-1 microperimeter (Nidek, Gamagori, Japan). This instrument has been previously described in detail.[19] For the purpose of this study, the following parameters were used: a fixation target consisting of red ring, 1° in diameter; white, monochromatic background at 4 apostilb (asb), stimulus size Goldman III, with 200 milliseconds projection time; and a customized radial grid of 45 stimuli covering the central 12° (centered on the fovea), 1° apart (inner stimuli), and 2° apart (outer stimuli). The starting stimulus light attenuation was set at 10 dB. A 4-2-1 double-staircase strategy was used with an automatic eye tracker that compensates for eye movements.[19,20] Pretest training was performed, and a 5-minute mesopic visual adaptation was allowed before starting the test. All subjects underwent microperimetry with dilated pupils. The mean RS was evaluated within central 4° and 12°, covering approximately 1 mm and 3 mm of central retinal area on the OCT map.

### *Treatment Protocols*

Macular laser treatment was performed after pupillary dilation and topical anesthesia according to the randomization assignment. The modified ETDRS treatment protocol was performed with a 514-nm green laser light (Coherent Novus Omni Laser, Coherent, Palo Alto, CA) with the following parameters: 100-$\mu$m spot size, 0.1-second duration, 80 mW to 100 mW power, and number of spots varying according to the extension of CSME. Treatment was performed up to 300 $\mu$m to 500 $\mu$m from the center of the foveal avascular zone.

Micropulse diode laser treatment was performed with a 810-nm diode laser (Iridex Oculite SLx, Iridex Corp., Mountain View, CA) with the following parameters: 125-$\mu$m spot size, 5% duty cycle of 0.2 seconds, 750 mW power, and number of spots varying according to the extension of CSME. Spots were delivered in a multiple and continuous fashion up to 250 $\mu$m to 300 $\mu$m from the center of the foveal avascular zone.

If needed, retreatment was performed according to the same protocol. Three months after any laser session, retreatment was considered if central subfield OCT macular thickness $\geq$250 $\mu$m, reduction of central subfield OCT macular thickening $<$50% from baseline, and BCVA decrease $>$5 letters on the ETDRS charts were observed.

### *Statistics*

To summarize the study parameters, we used the usual methods of descriptive statistics: mean value, standard deviation, and range for normally distributed quantitative variables (4° and 12° area RS); median, 25th (Ql) and 75th (Q3) percentiles for asymmetrically distributed quantitative variables (BCVA and OCT 1 mm); and frequency and percentages for qualitative variables (FAF). Treatment groups were compared at baseline using the Wilcoxon rank-sum test (BCVA and OCT 1 mm) and Student's *t*-test (4° and 12° RS). Time profiles of the two treatments were compared using two-way analysis of variance, with repeated measures focusing on the significance of the interaction time versus treatment effect. Because BCVA and OCT 1 mm showed abnormal frequency distribution (evaluated by the Shapiro—Wilk test), data were analyzed in terms of ranks. Retinal sensitivity values of both 4° and 12° areas have been analyzed in terms of original measures because of symmetric distribution of these parameters.

Within each treatment group, changes at the 12-month follow-up versus baseline values have been tested by means of the signed-rank test (BCVA and OCT 1 mm) and Student's *t*-test (4° and 12° RS). The association between treatment group and FAF distribution was analyzed by means of the Fisher exact test. All tests were 2-sided, with a significance level of 0.05. SAS software version 9.1.3 (SAS, Cary, NC) was used for all analyses.

Table 1. Baseline Clinical Characteristics of Study Groups

| Characteristic | MPDL (N = 32) | ETDRS (N = 30) |
|---|---|---|
| Age, Years, mean ± SD (range) | 62.8 ± 10.1 (31–81) | 62.1 ± 9.4 (45–77) |
| Years of DM, mean ± SD (range) | 20.1 ± 10.1 (2–38) | 13.8 ± 10.2 (2–37) |
| HbA1c, %, mean ± SD (range) | 8.9 ± 0.5 | 8.8 ± 0.4 |
| BCVA, log MAR* | | |
| Mean ± SD (range) | 0.21 ± 0.30 (0–1.20) | 0.29 ± 0.30 (0–1.00) |
| Median (Q1, Q3) | 0.09 (0, 0.26) | 0.22 (0.08, 0.43) |
| OCT 1 mm, $\mu$m† | | |
| Mean ± SD (range) | 358.3 ± 93.7 (251–690) | 378.4 ± 94.5 (255–615) |
| Median (Q1, Q3) | 341 (281, 383) | 386 (295, 421) |
| MP 4°, dB‡ | | |
| Mean ± SD (range) | 12.6 ± 4.1 (3.8–18.9) | 11.5 ± 4.5 (4.3–19.5) |
| Median (Q1, Q3) | 12.5 (9.2, 16.5) | 11.8 (7.3, 14.4) |
| MP 12°, dB§ | | |
| Mean ± SD (range) | 14.5 ± 3.0 (5.8–19.3) | 13.5 ± 3.5 (8.1–19.8) |
| Median (Q1, Q3) | 14.9 (12.4, 16.8) | 13.3 (11.0, 15.5) |

*$P$ = 0.1333, NS (Wilcoxon rank-sum test).
†$P$ = 0.2596, NS (Wilcoxon rank-sum test).
‡$P$ = 0.2908, NS (Student's $t$-test).
§$P$ = 0.2149, NS (Student's $t$-test).
SD, standard deviation; DM, diabetes mellitus; NS, not significant.

## Results

Of the 62 eyes included in this study (50 patients), 32 eyes underwent MPDL treatment, and 30 eyes underwent modified ETDRS laser treatment. All patients had type 2 diabetes mellitus, with a mean duration of 17.2 ± 10.2 years and a mean HbAlC of 8.8 ± 0.5%. The mean age of the patients was 62.7 ± 9.5 years. Before treatment, demographic and macular parameters were not significantly different between the two treatment groups (Table 1). Mean BCVA at baseline was 0.21 ± 0.3 logMAR in the MPDL group and 0.29 ± 0.3 logMAR in the ETDRS group (Wilcoxon rank-sum test, $P$ = 0.13), mean OCT central retinal thickness (CRT) was 358.3 ± 93.7 $\mu$m in the MPDL group and 378.4 ± 94.5 $\mu$m in the ETDRS group (Wilcoxon rank-sum test, $P$ = 0.26), mean central 4° RS was 12.6 ± 4.1 dB in the MPDL group and 11.5 ± 4.5 dB in the ETDRS group (Student's $t$-test, $P$ = 0.29), and mean central 12° RS was 14.5 ± 3.0 dB in the MPDL group and 13.5 ± 3.5 dB in the ETDRS group (Student's $t$-test, $P$ = 0.21; Table 1). There was no significant change in BCVA at each follow-up visit in either the MPDL or the ETDRS treatment group (signed-rank test, $P$ = 0.41 and $P$ = 0.82, respectively). Mean CRT significantly decreased at the 12-month follow-up in both groups (signed-rank test, $P$ = 0.0002 and $P < 0.0001$, respectively). Mean central 4° RS significantly increased at the 12-month follow-up in the MPDL group (mean increase, 0.74 ± 1.88 dB; Student's $t$-test; $P$ = 0.02), whereas it did not significantly change in the ETDRS treatment group (mean decrease, −0.72 ± 2.66 dB; Student's $t$-test; $P$ = 0.2). Mean central 12° RS significantly increased at the 12-month follow-up in the MPDL group (mean increase, 0.87 ± 1.89 dB; Student's $t$-test; $P$ = 0.0075), whereas it significantly decreased in the ETDRS treatment group (mean decrease, −1.69 ± 2.45 dB; Student's $t$-test; $P$ = 0.0026) (Table 2). Fundus autofluorescence never changed in all 32 eyes that underwent MPDL treatment even after retreatment. In all eyes that underwent ETDRS treatment, FAF showed a pattern of increased FAF (from the 1-month follow-up visit). The increased FAF pattern remained unchanged throughout the 3-, 6-, and 9-month follow-ups. At the 12-month follow-up, it changed to a decreased FAF pattern in 6 eyes (20%) and remained as an increased FAF pattern in 24 eyes (80%; Table 2). There was no significant difference in either BCVA or OCT CRT between the 2 treatment groups at 12 months (analysis of variance, $P$ = 0.48 and $P$ = 0.29, respectively). There was a significant difference in 4° and 12° central RS between eyes that underwent MPDL and ETDRS treatment (analysis of variance, $P$ = 0.04 and $P < 0.0001$, respectively; Figure 1).

The mean number of treatments was 2.03 ± 0.75 in the MPDL group and 2.1 ± 1 in the ETDRS treatment group. Fluorescein angiography did not show any sign of laser treatment in the MPDL treatment group, whereas laser scars were clearly visible in the ETDRS treatment group.

## Discussion

Subthreshold MPDL has gained increasing interest in the treatment of CSME, with promising results.[10,12,21]

Table 2. Descriptive Statistics of Study Parameters at Baseline and Each Follow-Up Visit: BCVA, OCT, CRT, Microperimetry, and FAF

| | MPDL (N = 32), Mean (SD, Median) | ETDRS (N = 30), Mean (SD, Median) |
|---|---|---|
| BCVA*, logMAR | | |
| Baseline | 0.22 (0.30, 0.09) | 0.29 (0.30, 0.22) |
| 1 month | 0.22 (0.28, 0.10) | 0.30 (0.28, 0.21) |
| 3 months | 0.23 (0.29, 0.12) | 0.32 (0.33, 0.20) |
| 6 months | 0.24 (0.32, 0.07) | 0.29 (0.27, 0.22) |
| 9 months | 0.22 (0.29, 0.10) | 0.30 (0.31, 0.20) |
| 12 months | 0.24 (0.25, 0.11) | 0.30 (0.30, 0.20) |
| Delta† | 0.02 (0.18, 0.01‡) | 0.002 (0.13, 0§) |
| OCT¶ 1 mm, $\mu$m | | |
| Baseline | 358.3 (93.7, 341) | 378.4 (94.6, 386) |
| 1 month | 349.1 (101.0, 327) | 376.8 (106.2, 352.5) |
| 3 months | 340.7 (114.4, 307) | 337.7 (72.3, 345.5) |
| 6 months | 345.7 (113.3, 321) | 327.3 (77.4, 306) |
| 9 months | 328.9 (94.5, 326) | 329.4 (80.0, 333.5) |
| 12 months | 311.7 (76.4, 389) | 310.4 (86.8, 301.5) |
| Delta† | −46.6 (73.5, −36‖) | −68.0 (79.6, −61.5**) |
| MP†† 4°, dB | | |
| Baseline | 12.7 (4.1, 12.5) | 11.5 (4.5, 11.9) |
| 1 month | 12.8 (4.3, 13.7) | 11.1 (5.0, 12.0) |
| 3 months | 12.7 (4.6, 13.5) | 11.0 (4.5, 10.0) |
| 6 months | 12.7 (4.5, 13.8) | 10.7 (4.7, 10.1) |
| 9 months | 13.1 (4.2, 13.7) | 10.5 (5.0, 9.4) |
| 12 months | 13.4 (4.2, 14.5) | 10.8 (5.2, 9.3) |
| Delta† | 0.74‡‡ (1.88, 0.35) | −0.72§§ (2.66, −1.10) |
| MP¶¶ 12°, dB | | |
| Baseline | 14.6 (3.0, 15) | 13.5 (3.5, 13.4) |
| 1 month | 14.8 (3.0, 15.4) | 12.8 (4.1, 12.8) |
| 3 months | 14.5 (3.0, 15.2) | 12.4 (4.0, 12.4) |
| 6 months | 14.8 (3.2, 15.8) | 12.2 (4.2, 11.4) |
| 9 months | 14.9 (3.3, 15.6) | 12.0 (4.4, 11.4) |
| 12 months | 15.4 (3.1, 16.1) | 11.8 (4.5, 11.2) |
| Delta† | 0.87‖‖ (1.89, 0.60) | −1.69*** (2.45, −1.55) |
| FAF†††, N (%) | | |
| Normal | 32 (100.0) | 0 (0.0) |
| Increased | 0 (0.0) | 24 (80.0) |
| Decreased | 0 (0.0) | 6 (20.0)‡‡‡ |

*$P$ = 0.4800, NS (ANOVA with repeated measures on rank-transformed observations, interaction time × treatment effect).
†Difference between 12-month and baseline values.
‡$P$ = 0.4137, NS (signed-rank test).
§$P$ = 0.8232, NS (signed-rank test).
¶$P$ = 0.2857, NS (ANOVA with repeated measures on rank-transformed observations, interaction time × treatment effect).
‖$P$ = 0.0002 (signed-rank test).
**$P < 0.0001$ (signed-rank test).
††$P$ = 0.0418 (ANOVA with repeated measures on observed values, interaction time × treatment effect).
‡‡$P$ = 0.0205,NS (Student's $t$-test).
§§$P$ = 0.2005, NS (Student's $t$-test).
¶¶$P < 0.0001$ (ANOVA with repeated measures on observed values, interaction time × treatment effect).
‖‖$P$ = 0.0075 (Student's $t$-test).
***$P$ = 0.0026 (Student's $t$-test).
†††Distribution of FAF at 12 months from treatment—all patients had ''Normal FAF'' at baseline. Fisher exact test, $P < 0.0001$.
‡‡‡All eyes in ETDRS group showed increased FAF from 1-month to 9-month follow-up.
ANOVA, analysis of variance; SD, standard deviation, NS, not significant.

It has been shown to be an effective treatment option, at least compared with modified ETDRS macular photocoagulation treatment.[2,11] In this prospective randomized study, we confirmed that subthreshold MPDL treatment was as effective as standard ETDRS argon laser photocoagulation in the treatment of CSME. In fact, BCVA and CRT determined with OCT did not significantly differ between the 2 treatment groups at

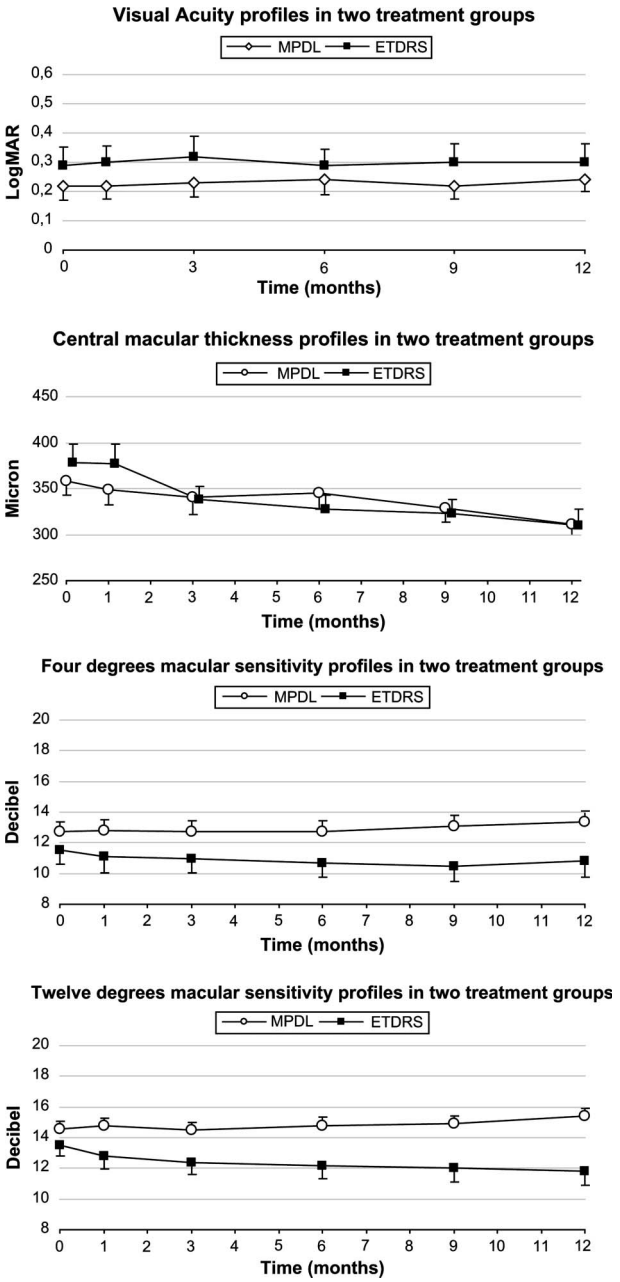


**Fig. 1.** Top, Graph showing BCVA changes expressed in logMAR at each follow-up visit (baseline and 1, 3, 6, 9, and 12 months) in the MPDL and the modified ETDRS laser photocoagulation treatment group. There was no significant difference between the 2 treatment groups at the 12-month follow-up ($P$ = 0.48). Upper middle, Graph showing central macular thickness changes determined by OCT and expressed in $\mu$m at each follow-up visit (baseline and 1, 3, 6, 9, and 12 months) in the MPDL and modified ETDRS laser photocoagulation treatment groups. There was no significant difference between the 2 treatment groups at the 12-month follow-up ($P$ = 0.29). Lower middle, Graph showing mean central 4° macular sensitivity changes determined by microperimetry and expressed in decibels at each follow-up visit (baseline and 1, 3, 6, 9, and 12 months) in the MPDL and modified ETDRS laser photocoagulation treatment groups. There was a significant difference in mean central 4° RS between the 2 treatment groups at the 12-month follow-up ($P$ = 0.04). Bottom, Graph showing mean central 12° macular sensitivity changes determined by microperimetry and expressed in decibels at each follow-up visit (baseline and 1, 3, 6, 9, and 12 months) in the MPDL and modified ETDRS laser photocoagulation treatment groups. There was a significant difference in mean central 12° RS between the 2 treatment groups at the 12-month follow-up ($P < 0.0001$).

the 12-month follow-up. Moreover, visual acuity remained stable, whereas CRT significantly decreased in both MPDL and ETDRS treatment groups. Recently, Figueira et al[12] reported a nonsignificant difference in BCVA between MPDL and ETDRS laser photocoagulation for CSME in a prospective, randomized, controlled trial. In the same study, the authors found a slight increase in CRT at the 12-month follow-up, although mean baseline retinal thickness of the patients they examined was much lower than that of our patients (—250 vs. 360 $\mu$m, respectively). These differences might explain the different OCT response to laser treatment.

In this study, we found a significant difference in RS and autofluorescence between the two treatment groups. In the MPDL treatment group, RS improved after treatment, whereas RS decreased in the ETDRS group, as shown by microperimetry. Moreover, decreased RS was detected particularly in the central 12° area covering the laser-treated area (Figures 2 and 3). Hudson et al[3] and Striph et al[7] have published sensitivity data, after macular laser photocoagulation for CSME, obtained with both conventional and short-wavelength perimetry. Those studies showed a significant decrease in 10° central RS after ETDRS macular laser photocoagulation in patients with CSME, suggesting that new treatment strategies that preserve both visual acuity and central visual function are needed.[3,7]

In a recent study, Bandello et al[8] reported that mean deviation in the central 10° sensitivity showed no significant difference between ''standard'' and ''light'' laser treatment groups at the 12-month follow-up when using a Nd:YAG 532-nm (frequency doubled) green laser. These authors reported that ''light'' laser treatment was aimed to obtain ophthalmoscopically barely visible burns at the level of the retinal pigment epithelium. Although these authors used standard perimetry, which may not be sensitive enough in determining shallow localized visual field loss in the macula, they documented that even barely visible laser burns irreversibly damage photoreceptors and decrease RS in the same way as the modified ETDRS photocoagulation treatment, at least up to the 1-year follow-up.[8] Retinal sensitivity data obtained with microperimetry add more detailed functional information in CSME that cannot be detected with simple visual acuity determination alone.[22,23] In fact, microperimetry data usually parallel patients' subjective perception, which may be useful in the clinical

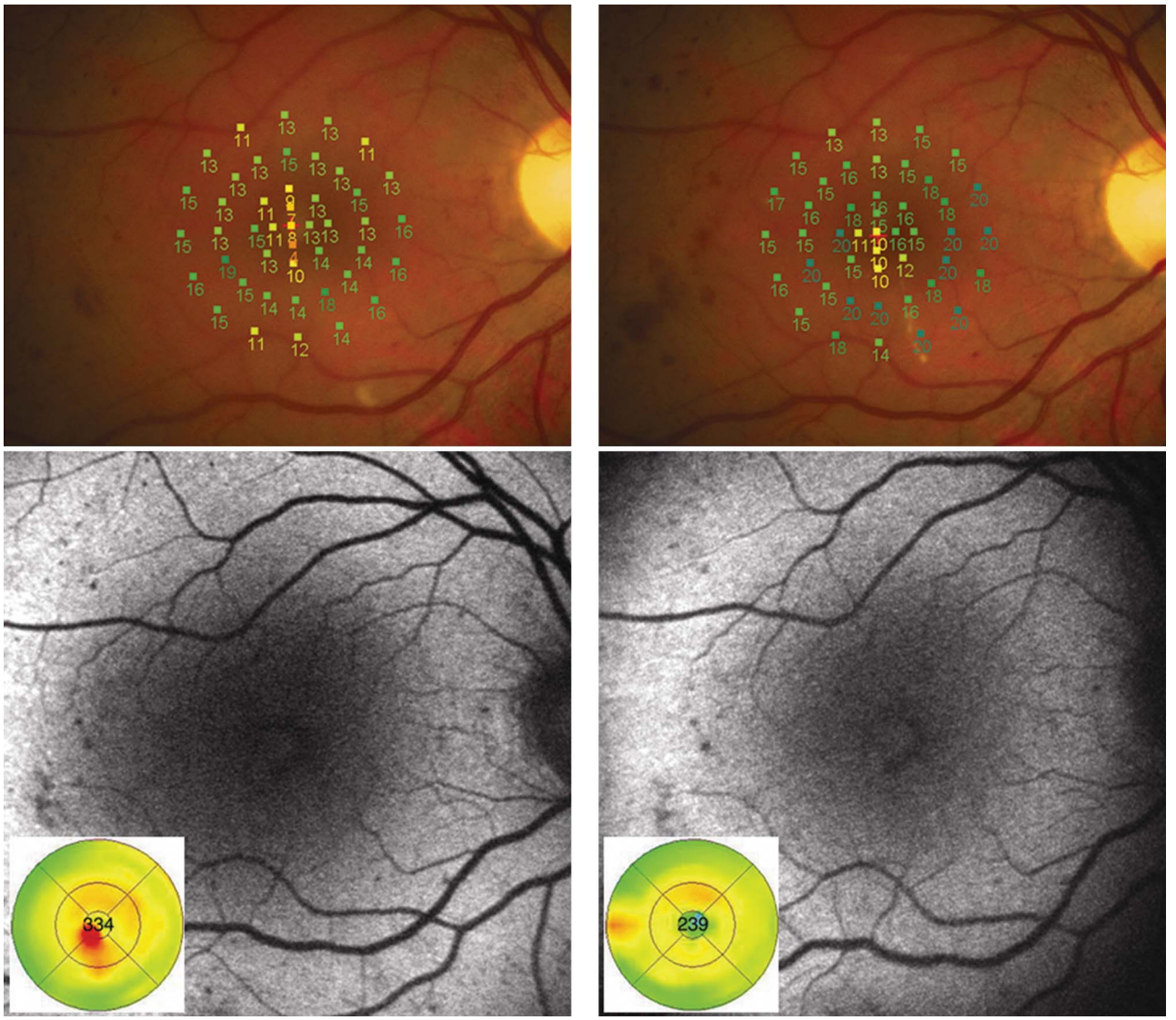


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**Fig. 2.** Baseline and 12-month follow-up of a patient with CSME treated with subthreshold MPDL photocoagulation. Top left, Microperimetry image consisting of an RS map, covering central 12° and overlapped on color fundus photograph before MPDL treatment. Bottom left, FAF and OCT retinal thickness map before MPDL treatment. Top right, Microperimetry image after MPDL treatment showing increased RS, both within the central 4° and 12° areas. Bottom right, FAF and OCT retinal thickness map after MPDL treatment showing no signs of MPDL photocoagulation on FAF and decreased retinal thickness on the OCT map.

management of these patients.[24] Therefore, the subthreshold laser photocoagulation treatment strategy, if proven to obtain at least the same morphologic results as conventional treatment, should be more widely used because functional data seem to support it.

Fundus autofluorescence showed no changes up to the 1-year follow-up in the subthreshold MPDL treatment group even after retreatment, whereas it showed spots of increased autofluorescence in the ETDRS treatment group. The pattern of increased FAF remained stable in 80% of the eyes up to the 12-month follow-up. However, in 20% of cases, the FAF pattern changed from increased to decreased FAF at 12 months. Fundus autofluorescence changes have previously been described after different retinal laser treatments.[17,25] Framme et al[17] found decreased FAF immediately after selective retinal pigment epithelium photocoagulation treatment for different macular diseases up to a 1-week follow-up. A decreased pattern of FAF changed to increased FAF and remained stable up to a 15-month follow-up.[17] In another study, Muqit et al[25] found a similar behavior of FAF patterns after medium-pulse pattern scanning laser (Pascal) treatment for diabetic macular edema using both ophthalmoscopically invisible or barely visible laser burns. These authors suggested that evolution of FAF

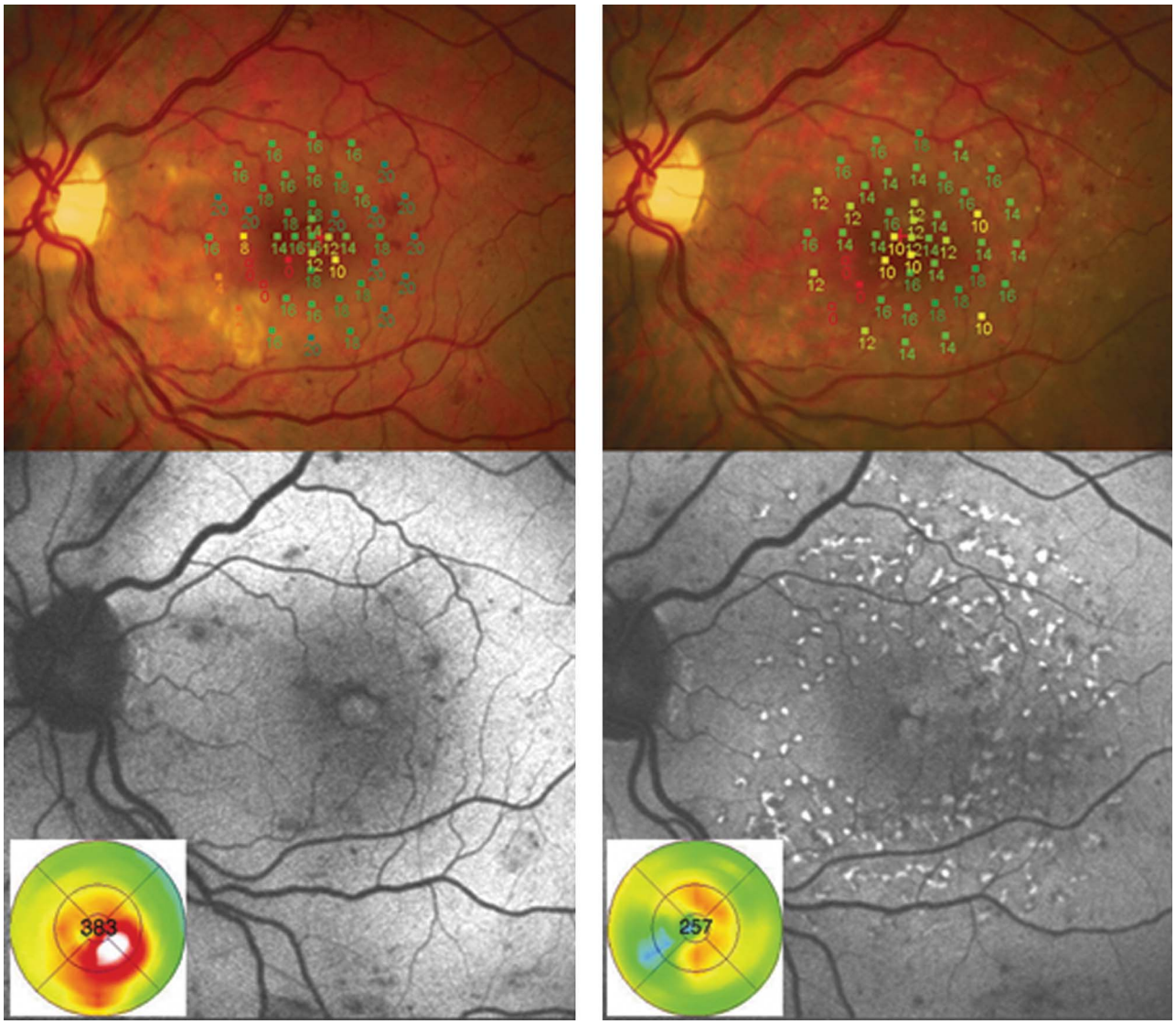


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**Fig. 3.** Baseline and 12-month follow-up of a patient with CSME treated twice with modified ETDRS grid laser photocoagulation. Top left, Microperimetry image consisting of an RS map, covering central 12° and overlapped on color fundus photograph before the modified ETDRS treatment. Bottom left, FAF and OCT retinal thickness map before the modified ETDRS treatment. Top right, Microperimetry image after the modified ETDRS treatment showing decreased RS (both within the central 4° and 12° areas, especially over the visible laser scars). Bottom right, FAF and OCT retinal thickness map after the second modified ETDRS treatment showing laser spots as areas of increased FAF and decreased retinal thickness on the OCT map.

over time may derive from an increased load of lipofuscin, which results from the coagulated photoreceptors and/or retinal pigment epithelium cells.[25] Therefore, the fact that no changes in FAF signal were found in this study in the MPDL group might indicate that there is no, or at least no currently clinically detectable, photoreceptor/retinal pigment epithelium cell damage even after multiple retreatment with subthreshold MPDL photocoagulation. The mechanism of action of MPDL is unknown, especially the effect of MPDL on pigment epithelium-derived factor.[26]

Major limitations of subthreshold MPDL photocoagulation treatment are no standardized parameters, difficulty in titration of treatment, and difficulty in documentation of treatment. In fact, we always used the same MPDL parameters as those proposed by Luttrull et al,[10] which might have influenced retinal thickness results, especially in patients with a higher OCT thickness value.

Although assessing the effect of MPDL photocoagulation treatment versus modified ETDRS protocol on visual acuity and OCT in patients with CSME was not the principal aim of this study, we found that it was

as effective as the modified ETDRS treatment in terms of visual acuity and CRT up to the 1-year follow-up. Fundus autofluorescence and microperimetry data have never been reported in patients treated with MPDL. Our FAF and microperimetry data are in favor of MPDL toward ETDRS photocoagulation treatment in patients with center-involving CSME. Additional studies on larger samples and with longer follow-ups are needed to assess standardized parameters and to better understand mechanisms of actions of MPDL photocoagulation treatment.

**Key words:** diabetic macular edema, fundus autofluorescence, laser treatment, micropulse diode laser, microperimetry, OCT.

## References

1. Klein R, Moss SE, Klein BE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. XI. The incidence of macular edema. Ophthalmology 1989;96: 1501–1510.
2. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study Research Group. Arch Ophthalmol 1985;103:1796–1806.
3. Hudson C, Flanagan JG, Turner GS, Chen HC, Young LB, McLeod D. Influence of laser photocoagulation for clinically significant diabetic macular edema (DMO) on short-wavelength and conventional automated perimetry. Diabetologia 1998;41:1283–1292.
4. Schatz H, Madeira D, McDonald HR, Johnson RN. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. Arch Ophthalmol 1991;109:1549–1551.
5. Lewis H, Schachat AP, Haimann MH, et al. Choroidal neovascularization after laser photocoagulation for diabetic macular edema. Ophthalmology 1990;97:503–510.
6. Guyer DR, D'Amico DJ, Smith CW. Subretinal fibrosis after laser photocoagulation for diabetic macular edema. Am J Ophthalmol 1992;113:652–656.
7. Striph GG, Hart WM Jr, Olk RJ. Modified grid laser photocoagulation for diabetic macular edema. The effect on the central visual field. Ophthalmology 1988;95:1673–1679.
8. Bandello F, Polito A, Del Borrello M, Zemella N, Isola M. ''Light'' versus ''classic'' laser treatment for clinically significant diabetic macular oedema. Br J Ophthalmol 2005;89: 864–870.
9. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Fong DS, Strauber SF, Aiello LP, et al. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. Arch Ophthalmol 2007;125:469–480.
10. Luttrull JK, Musch DC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. Br J Ophthalmol 2005; 89:74–80.
11. Olk RJ. Modified grid argon (blue-green) laser photocoagulation for diffuse diabetic macular edema. Ophthalmology 1986;93:938–950.
12. Figueira J, Khan J, Nunes S, et al. Prospective randomized controlled trial comparing subthreshold micropulse diode laser photocoagulation and conventional green laser for clinically significant diabetic macular oedema. Br J Ophthalmol 2009; 93:1341–1344.
13. Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and base-line patient characteristics. ETDRS report number 7. Ophthalmology 1991;98:741–756.
14. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94: 91–96.
15. Bartsch DU, Weinreb RN, Zinser G, Freeman WR. Confocal scanning infrared laser ophthalmoscopy for indocyanine green angiography. Am J Ophthalmol 1995;120:642–651.
16. Holz FG, Bellmann C, Margaritidis M, Schutt F, Otto TP, Volcker HE. Patterns of increased in vivo fundus autofluorescence in the junctional zone of geographic atrophy of the retinal pigment epithelium associated with age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1999;237: 145–152.
17. Framme C, Brinkmann R, Birngruber R, Roider J. Autofluorescence imaging after selective RPE laser treatment in macular diseases and clinical outcome: a pilot study. Br J Ophthalmol 2002;86:1099–1106.
18. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98:786–806.
19. Midena E, Radin PP, Pilotto E, Ghirlando A, Convento E, Varano M. Fixation pattern and macular sensitivity in eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. A microperimetry study. Semin Ophthalmol 2004;19:55–61.
20. Springer C, Bultmann S, Volcker HE, Rohrschneider K. Fundus perimetry with the Micro Perimeter 1 in normal individuals: comparison with conventional threshold perimetry. Ophthalmology 2005;l 12:848–854.
21. Laursen ML, Moeller F, Sander B, Sjoelie AK. Subthreshold micropulse diode laser treatment in diabetic macular oedema. Br J Ophthalmol 2004;88:1173–1179.
22. Vujosevic S, Midena E, Pilotto E, Radin PP, Chiesa L, Cavarzeran F. Diabetic macular edema: correlation between microperimetry and optical coherence tomography findings. Invest Ophthalmol Vis Sci 2006;47:3044–3051.
23. Vujosevic S, Pilotto E, Bottega E, Benetti E, Cavarzeran F, Midena E. Retinal fixation impairment in diabetic macular edema. Retina 2008;10:1443–1450.
24. Midena E. Fundus perimetry-microperimetry: an introduction. In: Midena E, ed. Perimetry and the Fundus: An Introduction to Microperimetry. Thorofare, NJ: Slack Incorporated; 2007:1–4.
25. Muqit MM, Gray JC, Marcellino GR, et al. Fundus autofluorescence and Fourier-domain optical coherence tomography imaging of 10 and 20 millisecond Pascal retinal photocoagulation treatment. Br J Ophthalmol 2009;93:518–525.
26. Ogata N, Tombran-Tink J, Jo N, Mrazek D, Matsumura M. Upregulation of pigment epithelium-derived factor after laser photocoagulation. Am J Ophthalmol 2001;132:427–429.