

# Serial Optical Coherence Tomography of Subthreshold Diode Laser Micropulse Photocoagulation for Diabetic Macular Edema

*Jeffrey K. Luttrull, MD; Charles J. Spink, MFA, CRA*

■ **BACKGROUND AND OBJECTIVE:** To use serial optical coherence tomography (OCT) to evaluate low-intensity, high-density subthreshold diode laser micropulse photocoagulation treatment of clinically significant diabetic macular edema.

■ **PATIENTS AND METHODS:** Eighteen consecutive eyes of 14 patients with clinically significant diabetic macular edema and a minimum foveal thickness of 223  $\mu\text{m}$  or greater were prospectively evaluated by OCT preoperatively and 1, 4, and 12 weeks following treatment.

■ **RESULTS:** Overall, estimated macular edema 3 months postoperatively (minimum foveal thickness – 223  $\mu\text{m}$ ) was reduced a mean of 24% ( $P = .02$ ).

Eleven eyes treated for recurrent or persistent clinically significant diabetic macular edema following prior treatment more than 3 months before study entry were most improved, with a mean reduction in estimated macular edema 3 months postoperatively of 59%. No treatment complications were observed. No patient demonstrated laser lesions following treatment.

■ **CONCLUSIONS:** Low-intensity, high-density subthreshold diode laser micropulse photocoagulation can reduce or eliminate clinically significant diabetic macular edema measured by OCT. Further study is warranted.

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## INTRODUCTION

Visible end point “threshold” or “suprathreshold” photocoagulation remains the primary treatment for diabetic macular edema, the most common cause of visual loss in patients younger than 60 years in developed countries.<sup>1</sup> The visible end point of conventional

photocoagulation represents the direct and indirect thermal tissue damage inherent to such treatment. It is not known whether such tissue damage is necessary to achieve the benefits of treatment. However, it is well known that such tissue damage is the cause of the many potential complications of conventional photocoagulation. These complications may result in both immediate and late visual loss, and limit the usefulness and effectiveness of visible end point photocoagulation.

New therapeutic approaches hold the promise of retina-sparing management of diabetic macular edema. These include use of pharmacologic agents and vitrectomy. Recently, a pilot study of subthreshold diode laser micropulse (SDM) photocoagulation for clinically

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*Drs. Luttrull and Spink are in private practice, Ventura, California.*

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*Address reprint requests to Jeffrey K. Luttrull, MD, 3160 Telegraph Road, Suite 230, Ventura, CA 93003.*

significant diabetic macular edema employing a new low-intensity, high-density treatment technique was reported.<sup>2</sup> Treatment was found to reduce diabetic macular edema despite the absence of an intraoperatively visible tissue-change end point. No laser-induced tissue damage was detectable clinically or angiographically at any point postoperatively.

Herein we describe the use of serial optical coherence tomography (OCT) to further evaluate the effectiveness of SDM photocoagulation for clinically significant diabetic macular edema.

## **PATIENTS AND METHODS**

Consecutive patients presenting with clinically significant diabetic macular edema for which macular photocoagulation treatment was indicated were invited to participate in the study. The study differed from usual and customary care in that patients were asked to return for OCT imaging 1 week and 1 month following photocoagulation treatment.

Exclusionary criteria included other significant macular disease such as age-related macular degeneration, uncontrolled or end-stage glaucoma, media opacity precluding adequate OCT, uncontrolled systemic hypertension, retinal photocoagulation or intraocular surgery within the previous 3 months, epiretinal membrane or vitreoretinal interface disease, intravitreal triamcinolone acetonide injection within 3 months, macular ischemia, failure to appear for consecutive follow-up visits, and failure to appear for the final 3-month post-treatment evaluation.

Study inclusion required clinically significant diabetic macular edema with a minimum foveal thickness of 223  $\mu\text{m}$  or more, determined using the "Fast Macula" scan mode of the OCT 2000 scanner (Zeiss Humphrey Instruments, Dublin, CA), and provision of informed consent for study participation. Patients with severe nonproliferative and proliferative diabetic retinopathy requiring SDM panretinal photocoagulation were included. Patients with recurrent or persistent clinically significant diabetic macular edema following prior conventional or SDM macular photocoagulation treated more than 3 months prior were also included.

Each patient underwent determination of best-corrected Snellen visual acuity, clinical biomicroscopic examination, intravenous sodium fluorescein angiogra-

phy, and OCT prior to the single session of photocoagulation treatment and at 3 months postoperatively.

Seventeen consecutive patients meeting study criteria were invited and elected to participate in the study. Of those, 3 eyes were subsequently disqualified after undergoing treatment: 1 for the development of macular ischemia and 2 for the development of severe or malignant hypertension requiring hospitalization and resulting in marked generalized worsening of their background diabetic retinopathy. In total, 18 eyes of 14 consecutive patients successfully completed the study (Table).

### **Patient Treatment History Prior to Study Entry**

Seven eyes in the study underwent first time treatment for clinically significant diabetic macular edema. One eye had had prior panretinal photocoagulation for proliferative retinopathy. One eye had been treated with intravitreal triamcinolone acetonide for clinically significant diabetic macular edema more than 3 months prior to study entry, with recurrence of clinically significant diabetic macular edema. Four eyes had undergone prior conventional argon laser macular photocoagulation. Ten eyes had undergone prior SDM photocoagulation for clinically significant diabetic macular edema. Four of these eyes were treated in the study for recurrence of clinically significant diabetic macular edema following prior successful SDM photocoagulation or conventional argon laser macular photocoagulation performed more than 6 months prior to study entry. Seven eyes were treated for persistent clinically significant diabetic macular edema following prior SDM photocoagulation performed 3 to 4 months prior to study entry. Altogether, 11 of 18 eyes (61%) had undergone treatment for clinically significant diabetic macular edema prior to entering the study.

### **Low-Intensity, High-Density SDM Treatment Protocol and Technique**

All SDM photocoagulation treatment was performed by a single surgeon (JKL). Informed consent was obtained and topical anesthesia was administered. A 0.96 $\times$  inverted image ophthalmoscopic contact lens (Mainster Focal/Grid; Ocular Instruments, Bellevue, WA) was applied to the cornea.

An 810-nm diode laser photocoagulator (Iris Medical OcuLight SLx; IRIDEX Corporation, Mountain View, CA) was used in its MicroPulse operating mode, a feature that allows improved control and spatial con-

TABLE  
**Serial Optical Coherence Tomography of Subthreshold Diode Laser Micropulse Photocoagulation for Clinically Significant Diabetic Macular Edema 3 Months Following Treatment**

Patient No.	Prior Treatment History	Eye	MFT		Thickness Change		EME*		MEI*
			Preop	3 Mo. Postop	( $\mu\text{m}$ )	(%)	Preop	3 Mo. Postop	
21	new CSME	OD	253	275	-22	-9	68	90	-32%
21	new CSME	OS	243	250	-7	-3	58	65	-12%
30	new CSME	OS	448	405	43	10	263	220	16%
2	new CSME	OD	354	262	92	26	169	77	54%
2	new CSME	OS	240	365	-125	-52	55	180	-227%
19	new CSME	OS	569	636	-67	-12	384	451	-17%
25	k, a1, s6, r	OS	236	159	77	33	51	-26	151%
7	s2, p	OD	286	191	95	33	101	6	94%
8	a1, s2, p	OD	231	191	40	17	46	6	87%
11	a1, s2, p	OD	325	305	20	6	140	120	14%
32	s1, p	OS	253	269	-16	-6	68	84	-24%
14	s8, p, †	OD	457	373	84	18	272	188	31%
20	s4, p	OD	378	329	49	13	193	144	25%
20	s6, p	OS	461	263	198	43	276	78	72%
17	s2	OD	616	364	252	41	431	179	58%
17	new CSME	OS	289	277	12	4	104	92	12%
28	s2, r	OS	301	307	-6	-2	116	122	-5%
15	a1, r	OS	306	135	171	56	121	-50	141%
Max. edema (reduction)			616	636	252	56	46	-50	151%
Min. edema (reduction)			231	135	-125	-52	431	451	-227%
Mean			347	298	49	12	162	113	24%
Improved eyes		12		mean	94	23	mean	86	63%
Worsened eyes		6		mean	-30	-12	mean	165	-45%
Eyes unchanged		0							

MFT = minimum foveal thickness; EME = estimated macular edema (MFT - 185  $\mu\text{m}$ ); Preop = preoperative; Postop = postoperative; MEI = percent change in EME; new CSME = new clinically significant diabetic macular edema, no prior laser treatment; OD = right eye; OS = left eye; k = intravitreal triamcinolone acetonide more than 3 months prior; a = prior conventional macular photocoagulation; s = prior subthreshold diode laser micropulse macular photocoagulation; r = recurrent CSME; p = persistent CSME, prior laser treatment within 4 months of study entry.

\*185  $\mu\text{m}$  threshold.

†Prior panretinal photocoagulation.

finement of laser-induced photothermal effects to the retinal pigment epithelium to minimize the thermal spread and collateral damage to the overlying neurosensory retina.<sup>3-8</sup> All patients were treated with the same micropulse peak power of 0.8 W and aerial spot size of 125  $\mu\text{m}$ , which, with the 0.96 $\times$  contact lens,

produced on the retina a spot diameter of 130  $\mu\text{m}$  with a micropulsed irradiance of 6,000 W/cm<sup>2</sup>. Exposure duration and duty cycle were adjusted depending on patients' pigmentation.

Eyes with a lightly pigmented fundus (generally white) were treated with applications of 0.15 second

exposure duration at 15% duty cycle, each delivering a train of 75 sequential laser pulses of 300  $\mu\text{s}$  "ON" time separated by 1,700  $\mu\text{s}$  "OFF" time (15% duty cycle). Eyes with darker fundi (generally Asian or Hispanic) were treated with applications of 0.10 second exposure duration at 10% duty cycle, each delivering a train of 50 sequential laser pulses of 200  $\mu\text{s}$  "ON" time separated by 1,800  $\mu\text{s}$  "OFF" time (10% duty cycle).

Guided by the preoperative OCT, all areas of visible macular thickening were treated with confluent applications up to the edge of the fovea and surrounding the fovea if thickened. Due to the absence of any visible end point, confluent laser applications were often repeated two to three times during a given treatment session to ensure complete coverage of the edematous area. The laser treatment parameters, number of applications, and complications of treatment were recorded for each patient.

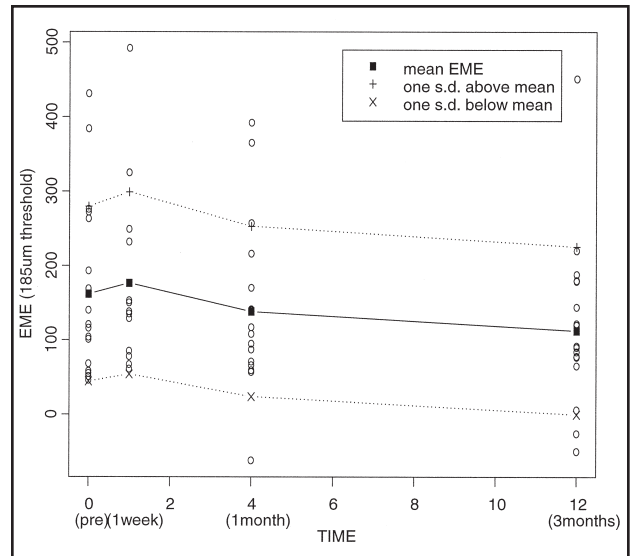
In a manner akin to that recently reported by Chan and Duker, the "estimated macular edema" (minimum foveal thickness - 185  $\mu\text{m}$ ) and "macular edema index" (percent change in estimated macular edema) were calculated for each eye at each follow-up interval based on the OCT findings<sup>9</sup> (Table).

## RESULTS

The number of SDM macular laser applications ranged from 687 to 1,942 per eye (mean = 1,060 applications). No treatment complications were observed. No patient demonstrated clinically visible or angiographically detectable laser lesions at any point postoperatively.

Overall, visual acuity was unchanged. Preoperative minimum foveal thicknesses ranged from 231 to 616  $\mu\text{m}$  (mean = 347  $\mu\text{m}$ ). One week following treatment, there was no significant change in mean minimum foveal thickness ( $P = .3$ , paired  $t$  test). One month following treatment, mean minimum foveal thickness was reduced 30  $\mu\text{m}$  and mean estimated macular edema was reduced 12%. This improvement was not statistically significant ( $P = .08$ ).

Three months following SDM photocoagulation, 12 of 18 treated eyes (67%) were improved, demonstrating reduced minimum foveal thickness by OCT. Overall, minimum foveal thickness 3 months after treatment ranged from 135 to 636  $\mu\text{m}$  (mean = 298  $\mu\text{m}$ ). Minimum foveal thickness change ranged from an increase of 125  $\mu\text{m}$  (52%) to a reduction of 252  $\mu\text{m}$  (40%), for a mean



**Figure.** Scatterplot of estimated macular edema (EME) versus time (0 = preoperative to 3 months postoperative). EME = minimum foveal thickness - 185  $\mu\text{m}$ ; s.d. = standard deviation.

minimum foveal thickness reduction of 49  $\mu\text{m}$  (12%). Estimated macular edema 3 months after treatment ranged from an increase of 227% to a decrease of 151%, for a mean reduction of 24%. This mean decrease in minimum foveal thickness 3 months following SDM photocoagulation for clinically significant diabetic macular edema was statistically significant ( $P = .02$ ) (Table and Figure).

Of eyes treated for the first time for clinically significant diabetic macular edema, only 3 of 7 (43%) were improved 3 months postoperatively. Overall, these 7 eyes had a mean 29% worsening of their estimated macular edema. In contrast, 8 of 10 eyes (80%) having undergone a range of 1 to 8 prior SDM treatment sessions (mean = 3.5 treatments), and 9 of 11 eyes (82%) having undergone any prior macular photocoagulation for clinically significant diabetic macular edema, were improved. Overall, these previously treated eyes had a mean 59% reduction in their estimated macular edema 3 months following re-treatment with SDM photocoagulation.

## DISCUSSION

The incidence and prevalence of diabetes mellitus and its complications continue to increase. Effective management of diabetic macular edema is thus of immense importance with regard to the public and economic health of developed countries. Great strides have been made in the management of ocular compli-

cations of diabetes mellitus in recent decades. We are in the midst of a revolution in the care of many retinal diseases, including diabetic retinopathy. New pharmacologic therapies and minimally invasive surgical interventions, such as 25-gauge vitrectomy and endoscopy, hold promise. However, laser photocoagulation remains the mainstay of treatment for the complications of diabetic retinopathy.

Conventional threshold photocoagulation with a visible treatment end point is inherently destructive to the retina. Therefore, although the benefits of such treatment are well-known, so are the inherent risks that may lead to short-term and long-term visual loss. Attempts have been made to administer effective photocoagulation while reducing tissue damage and thus the risks of treatment. Such attempts, generally made by reducing conventional continuous wave laser photocoagulation intensity, have met with qualified success. Conventional threshold photocoagulation at the lowest energy to produce a barely visible intraoperative end point, and even intraoperatively clinically invisible "subthreshold" photocoagulation, still typically produce demonstrable tissue damage clinically, angiographically, or both. Thus, the risks of treatment, although possibly attenuated, remain. However, as recently reported by Bandello et al., it also appears that conventional photocoagulation treatment intensity can be significantly reduced without loss of clinical effectiveness.<sup>10</sup>

Recently, two studies reported that micropulsed 810-nm diode laser photocoagulation administered with no intraoperatively visible end point can reduce or eliminate clinically significant diabetic macular edema without producing ophthalmoscopically or fluorescein angiographically detectable tissue damage in eyes with extended follow-up.<sup>2,11</sup> In this study, we evaluated SDM laser treatment for clinically significant diabetic macular edema in a prospective, nonrandomized fashion using OCT as an objective quantitative and reproducible measure of treatment response.

Similar to other recently described approaches, we elected to use the minimum foveal thickness determined by OCT as the measure of macular thickening and treatment response.<sup>9</sup> Although clinically significant diabetic macular edema may be present without central foveal edema, the minimum foveal thickness measurement is the most sensitive OCT measure of macular thickness change. Measurements of larger

macular areas, such as the 1.0-mm central foveal zone average thickness and total macular volume, may miss or minimize local changes in macular thickness to the point of being difficult to detect and follow.<sup>8</sup> This may explain, at least in part, the lack of demonstrable OCT improvement in response to clinically effective macular photocoagulation treatment for clinically significant diabetic macular edema in at least one prior study.<sup>9</sup>

Although diurnal variation has been observed, reproducibility of such OCT measures has been found by prior studies to be good.<sup>12-14</sup> We chose 185  $\mu\text{m}$  as the upper limit of a normal minimum foveal thickness (Wisconsin Photographic Reading Center standard), which is two standard deviations above the mean minimum foveal thickness found in studies of normal patients.<sup>15,16</sup> Prior studies have suggested that macular thickening of less than 30% to 50% is difficult to reliably identify clinically.<sup>17-20</sup> Thus, we elected to select patients with a minimum foveal thickness of greater than 120% of 185  $\mu\text{m}$  (222  $\mu\text{m}$ ) to both approximate the clinically observable macular thickening followed in the SDM photocoagulation pilot study and allow for a positive treatment response readily observable by OCT.<sup>2</sup> Prior studies have reported that patients with diabetes mellitus without retinopathy or clinically significant diabetic macular edema may have a minimum foveal thickness of greater than 185  $\mu\text{m}$ , as may normal males compared to females.<sup>21-23</sup> Thus, in choosing 185  $\mu\text{m}$  as the minimum foveal thickness upper limit of the normal standard, we have been conservative, possibly overestimating the degree of diabetic macular edema (estimated macular edema) and underestimating any positive treatment effect.<sup>9</sup>

Patients with other macular disease and other potential causes of macular edema were excluded from this study. However, inclusion criteria for this study were somewhat liberal.<sup>10</sup> Patients having undergone intraocular surgery within 3 months of study entry were excluded, but given the prolonged healing response often observed in patients with diabetes mellitus, a longer exclusionary period may have been more appropriate. Patients with other typically poor prognostic factors were included in this study, such as patients with (1) prior laser treatment for macular edema (conventional or SDM), (2) recurrent or persistent macular edema, (3) severe nonproliferative and proliferative diabetic retinopathy, (4) diffuse clinically significant diabetic macular edema, and (5) cystoid foveal edema. It is also important to recognize

that not all patients with clinically significant diabetic macular edema have central foveal edema.

By selecting only patients with central foveal thickening, we studied patients with a generally poorer visual and anatomic prognosis, and did not consider eyes to have been successfully treated that may have demonstrated overall reductions in macular edema without improvement in central foveal swelling.<sup>10,22,24,25</sup> Finally, although two patients were eliminated from the study due to the development of severe uncontrolled hypertension, study patients were not monitored for systemic blood pressure, blood sugar levels, and hemoglobin A1c levels. When elevated, each of these factors may be associated with a poorer clinically significant diabetic macular edema treatment response and visual prognosis.<sup>10,26</sup>

Despite these limitations, according to postoperative changes in minimum foveal thickness measured by OCT, this study demonstrated reduction or elimination of diabetic macular edema by SDM photocoagulation. This corroborates the findings of the recent clinical pilot study.<sup>1</sup> In addition, the reduction of clinically significant diabetic macular edema by SDM photocoagulation in this study appears similar in magnitude to that reported previously for conventional photocoagulation, pharmacologic intervention, or vitrectomy.<sup>20,27-30</sup>

Of particular note is the observation that the response to SDM photocoagulation in this study was most positive in patients having undergone prior SDM photocoagulation. Such eyes might actually be expected to have a poorer treatment prognosis, in that they have failed to respond fully to previous treatment attempts. However, this finding is consistent with theoretical hypotheses regarding the biophysics of low-intensity photocoagulation, which predict a cumulative treatment effect.<sup>6-8</sup> This observation also further corroborates the pilot study in which eyes with clinically significant diabetic macular edema were treated every 3 to 4 months as necessary until there was clinical resolution of the clinically significant diabetic macular edema. Indeed, the eye reported in this study with the worst outcome at 3 months following initial SDM photocoagulation (Eye No. 2, right eye) with a 227% increase in estimated macular edema at 3 months postoperatively) enjoyed complete resolution of clinically significant diabetic macular edema and improved visual acuity following additional SDM treatment sessions performed over the ensuing 6 months (JKL, unpublished data).

As in the pilot study, no complications of treatment were observed. Despite the high density of the laser applications, with more than 19,000 SDM applications in the 18 study eyes, no patient demonstrated any clinically visible or angiographically detectable laser lesion at any point postoperatively. With an end point of clinical response rather than intraoperatively visible retinal damage, SDM photocoagulation may uniquely permit an "as necessary" macular photocoagulation re-treatment regimen, without concern for cumulative tissue damage that could limit re-treatment, such as results from conventional photocoagulation, but which does not occur following SDM photocoagulation.

This study has many limitations, from its design to the sample size. Due to the small number of subjects, each eye was viewed individually for statistical analysis despite several bilateral cases, a potential source of error. Due to deliberate avoidance of intraoperatively visible end point, SDM laser parameters cannot be titrated at the time of treatment and the optimal parameters remain unknown. The parameters chosen for this study were empirically derived from clinical experience (JKL), early clinical reports,<sup>14,31-34</sup> experimental studies,<sup>3-5</sup> and theoretical considerations.<sup>2,6-8</sup> Nonetheless, the favorable clinical responses to the treatment parameters reported here and previously demonstrate that therapeutic thermal effects occur without ophthalmoscopically or fluorescein angiographically demonstrable tissue damage.<sup>2</sup> The treatment effect appears to be cumulative, enhanced by multiple SDM treatments over time, which are permitted by the absence of treatment-associated tissue damage.

OCT has become an essential tool in the diagnosis and management of diabetic macular edema. However, conventional macular photocoagulation treatment paradigms antedate OCT. Reconciliation of conventional treatment approaches with the new diagnostic information provided by OCT remains a challenge for clinicians.<sup>35</sup> Because the risks of macular photocoagulation with SDM treatment appear to be reduced, early treatment of diabetic macular edema not meeting Early Treatment Diabetic Retinopathy Study criteria for clinically significant diabetic macular edema, possibly evident by OCT alone, may be permitted and may be of benefit to patients with diabetes mellitus. Further study of SDM photocoagulation in the management of diabetic retinopathy and other retinal vascular diseases appears indicated.

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