# In Vivo Retinal Morphology after Grid Laser Treatment in Diabetic Macular Edema

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***Purpose:*** To analyze immediate in vivo intraretinal morphologic changes secondary to standardized grid photocoagulation using spectral domain optical coherence tomography (SD OCT).

***Design:*** Prospective clinical trial.

***Participants:*** Thirteen consecutive patients with treatment-naïve clinically significant diabetic macular edema (DME).

***Methods:*** Before and 1 day after standardized grid photocoagulation using the PASCAL system (Pattern Scan Laser, OptiMedica Corporation, Santa Clara, CA), Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) examinations based on an eye-tracking system, infrared fundus imaging, color fundus photography, and biomicroscopy were performed. A standardized visual acuity assessment (Early Treatment Diabetic Retinopathy Study protocol) and fluorescein angiography were performed at baseline.

***Main Outcome Measures:*** Morphologic changes secondary to grid laser treatment.

***Results:*** One day after laser therapy, immediate morphologic alterations of only the outer retinal layers, that is, the retinal pigment epithelium (RPE), the photoreceptor layer (PRL), and the outer nuclear layer (ONL), were observed. The shape of the laser-induced lesions did not show a sagittal alteration pattern throughout all 3 of the layers, however, but rather seemed to follow an oblique pathway throughout the ONL, changing direction at the level of the external limiting membrane and proceeding sagittally through the PRL and RPE. These morphologic changes also induced biometric changes, such as a decrease in central retinal thickness combined with local thickening at the lesion site, especially in the PRL.

***Conclusions:*** Spectral domain optical coherence tomography provides new insight into the immediate morphologic changes after laser treatment using the PASCAL laser system. Standardized grid photocoagulation induces characteristic homogenous alteration in the neurosensoric retinal layers. Biometric changes, indicating an immediate effect, were observed within 1 day after treatment.

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A main cause of significant visual impairment in patients with diabetes mellitus is diabetic macular edema (DME), a severe, but characteristic and frequent complication of diabetic maculopathy.[1] The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported a 10-year incidence of DME between 13.9% and 25.4% with a poor long-term prognosis.[2]

The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that focal laser photocoagulation, the previous gold standard therapy, reduces moderate vision loss caused by DME by 50% or more.[3] The specific mechanisms by which focal photocoagulation reduces DME, however, remain unknown. It is not clear whether the therapeutic effect, measured as reduced retinal blood flow, is caused by therapeutically induced improvements in retinal tissue oxygenation,[1–4] overall reduced retinal tissue, or biochemical changes at the level of the retinal pigment epithelium (RPE).[4–6] Furthermore, the precise role of laser energy in photocoagulation for DME is a matter of controversy.[7–10]

The PASCAL (Pattern Scan Laser, OptiMedica Corporation, Santa Clara, CA), a photocoagulator offering a fully integrated pattern scan laser system designed to treat retinal diseases using a predetermined pattern array, is a new development in the field of retinal laser photocoagulation.[11] A large number of identical spots can be applied by 1 foot-pedal depression, which keeps the treatment parameters constant during the entire laser procedure at each treatment spot location. Spot size uniformity and spot placement precision are produced by using identical and reproducible laser power settings, which result in reproducible morphologic effects at all spot locations. Photocoagulation is performed by irradiation with a frequency-doubled Nd:YAG laser diode having a 532-nm wavelength. This new technique permits several laser coagulations to be performed in a grid pattern around the fovea in a standardized and reproducible manner.

Optical coherence tomography (OCT) has become an important tool over the last decade in the diagnosis of DME because the retinal morphology can be evaluated in detail, similar to in vivo histology. Conventional OCT imaging, however, is based on 6 radial cross-sectional scans, and the information obtained is therefore limited to a few randomly selected locations and an overall low resolution of the



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structural details. The fourth-generation OCT, SD OCT, uses a fast spectral domain technique and performs scans in a raster pattern throughout the entire macular area at a resolution of 5 $\mu$m in the axial and 20 $\mu$m in the transverse direction. Thus, the retinal morphology can be imaged at all locations transversely and can be located to all retinal layers axially. These advances in OCT technology can provide novel insight into the in vivo changes that occur in the human retina secondary to laser treatment. Another recent development in OCT imaging is the combination of the fourth-generation system with an eye tracking system. The main advantages of this combination, realized in the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), are improved imaging quality and the ability to observe morphologic changes in exactly the same retinal location over time. This combination produces a dedicated diagnostic imaging tool that enables the analysis of intraretinal changes secondary to laser treatment over time.

The present study analyzed immediate morphologic changes in the human retina after a standardized grid laser treatment using standardized SD OCT examinations.

## Materials and Methods

The study was performed at the Department of Ophthalmology of the Medical University of Vienna. All the research and measurements adhered to the tenets of the Declaration of Helsinki, the study was approved by the local ethics committee, and informed consent was obtained from all individuals after a detailed discussion of the nature and possible consequences of the study procedures.

Thirteen consecutive patients (9 men, 4 women; mean age 58±10 years) with diabetic maculopathy showing generalized clinically significant macular edema (DME) associated with diabetes mellitus type 2 were included in the study. All patients were treatment naïve or had not received any treatment for DME at least 3 months before inclusion.

Color fundus photography and Spectralis OCT (Heidelberg Engineering) examinations for imaging structural and biometric retinal changes secondary to macular grid laser treatment with time and biomicroscopy were performed at baseline and day 1. Retinal thickness measurements by OCT were defined as a thickness change in the central millimeter of the ETDRS grid and performed at the same time of the day (late morning) based on the possible diurnal fluctuation of the extent of DME.[12] In addition, patients were examined using a standardized protocol (ETDRS) for the assessment of best-corrected visual acuity and by fluorescein angiography at baseline.

In all patients, the PASCAL system[11] was used, which is designed to treat retinal diseases using a single spot or a predetermined pattern array of up to 56 spots. Before the laser procedure, pupillary dilatation was induced by topical application of 1% tropicamide (Mydriaticum "Agepha," AGEPHA GmbH, Vienna, Austria) and 2.5% phenylephrine hydrochloride eyedrops. Topical oxybuprocaine 1% (manufactured by the institutional pharmacy) was instilled immediately before treatment initiation.

As recommended for the modified ETDRS grid laser treatment, patients with DME received a predetermined grid pattern laser treatment of the edematous perifoveolar region in this study setting consisting of 56 laser lesions performed in a homogenous ring pattern after energy titration using the PASCAL laser system.[3,6] In addition, single microaneurysms were coagulated with single laser lesions. In 1 patient, the grid laser treatment was performed using a single spot laser treatment. A 10-ms burn duration and a 100-$\mu$m diameter laser spot size were chosen as standard laser settings, and the treatment was performed using an Area Centralis Laser Lens (Volk, Mentor, OH). In all patients, the laser power was determined on the basis of ophthalmoscopic visibility of the treatment spot and adjusted to a spot of light grayish color observed clinically.

## Results

The mean ETDRS visual acuity score for the 13 patients was 74±8. All patients had generalized clinically significant macular edema secondary to type 2 diabetes mellitus.

### Morphologic Retinal Changes

The characteristic changes typically seen in DME, such as cyst formation and diffuse swelling in the inner nuclear layer and outer nuclear layer (ONL), were observed in all patients.[13] Additional subfoveolar subretinal fluid was observed in 4 patients.

Morphologic changes secondary to the retinal grid photocoagulation were observed on day 1. In all patients, each laser lesion was visible as a clear alteration at the level of the RPE, the photoreceptor layer (PRL), and to a lesser extent, the ONL. No specific changes of the inner retinal layers were observed. The shape of the laser lesions did not show a sagittal alteration pattern throughout the outer retinal layers as expected, but rather seemed to have an oblique pathway throughout the ONL, changing direction at the level of the external limiting membrane (ELM) and proceeding sagittally in the PRL and RPE.

A representative example of these characteristic effects is shown in Figure 1. Before laser treatment (image indicated as baseline), small areas of bleeding were observed in the infrared image (left), and there were large intraretinal cystoid changes in the ONL and inner nuclear layer, as well as subretinal fluid beneath the fovea in the OCT image (right). One day after laser treatment (indicated as day 1), the laser lesions were slightly visible on infrared photography (left) and clearly visible in the corresponding OCT scan (right) as diagonal alterations of the ONL, changing their orientation at the border of the ELM. The red boxes indicate areas of magnification shown below. All lesions seemed to have followed a concentric pathway throughout the outer retinal layers, heading toward the center of the grid pattern. This characteristic oblique and concentric laser lesion pattern was observed in all patients on day 1. The infrared and OCT findings on day 1 of 3 other patients are shown in Figure 2.

Because it was not clear whether these unexpected changes were due to the specific PASCAL grid pattern used to perform several laser spots at nearly the same time, in 1 patient the laser grid treatment was performed with a single laser spot. In this patient as well, however, similar changes were observed (Fig 3). Furthermore, it was not clear whether a single laser lesion would cause the same morphologic characteristics. Thus, in 2 patients the grid laser treatment was performed in 2 steps, first placing 1 single laser lesion and analyzing its effects on morphology in OCT, and second completing the grid photocoagulation as explained above. The results showed that even a single laser lesion caused comparable intraretinal changes that did not change in size or position because of the grid completion (images not shown).

### Biometric Retinal Changes

At baseline, mean central retinal thickness (CRT) measured in the central millimeter was 436±124 $\mu$m. On day 1, mean CRT was 434±119 $\mu$m ($P = 0.7$). The CRT was decreased in 7 patients